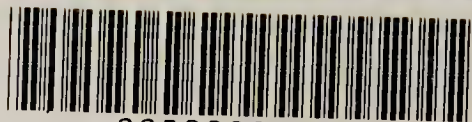




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XXXI. *On the Early Stages of Inflammation.* By JOSEPH LISTER, Esq. F.R.C.S. Eng. and Edin., Assistant Surgeon to the Royal Infirmary, Edinburgh. Communicated by Dr. SHARPEY, Sec. R.S.

Received June 18,—Read June 18, 1857.

#### INTRODUCTION.

THE morbid process designated by the term Inflammation, being one to which every organ and probably every tissue of the body is liable, and comprehending as it does in its progress and consequences by far the greater number of the ills to which flesh is heir, possesses a deeper interest for the physician or surgeon than any other material subject which could be named. The practical importance of inquiries tending to elucidate the essential nature of this process, has been for centuries recognized by all enlightened members of the medical profession; for it is obvious that just views regarding it must tend to promote the establishment of sound principles in the treatment of the diseases which it produces. At the present day more especially, when theory is allowed such free scope, and is permitted to attack the most time-honoured rules of practice, we stand in peculiar need of the beacon-light of correct pathology to enable us to steer a safe course amid the various conflicting opinions which assail us. Yet so far from our knowledge of inflammation being in a satisfactory condition, authorities are at variance upon the fundamental question, whether it is to be regarded, in accordance with JOHN HUNTER'S opinion, as active in its nature, and consisting in an exaltation of the functions of the affected part, or whether it should not rather be considered a passive result of diminished functional activity.

In seeking for the solution of this great problem, we cannot expect to gain much from the contemplation of the advanced stages and results of inflammation, such as copious exudation of lymph, suppuration, ulceration, or gangrene. When any one of these has taken place, the nature of the original disease is masked to a great extent by the subsequent changes; and the cell-development which occurs in lymph after its effusion, is no more proof of activity in the inflammatory process, than the loss of the vital powers in gangrene can be accepted as evidence in the opposite direction. It is upon the first deviations from health that the essential character of the morbid state will be most unequivocally stamped, and it is therefore to the early stages of inflammation that attention must be chiefly directed in this inquiry.

If the palm of the hand be chafed by long-continued friction, as for example in rowing a boat, the first thing that will be observed, when attention has been directed to the part by a feeling of uneasiness, will be that the skin is redder than natural, implying



that the vessels are abnormally loaded with blood, and if the irritation be continued, the cuticle will be raised in the form of a blister. If, now, the loosened epidermis be artificially removed on the earliest occurrence of effusion, a scarlet raw surface will be exposed; and on pressing the tender dermis firmly with the finger, and suddenly removing the pressure, it will be found that while the redness will for the most part have momentarily disappeared, there will be many minute red points from which the blood cannot be expelled. This shows that, while the blood is in part still free to move, there are some minute vessels completely clogged with it. Again, if a portion of mustard be placed on the skin covering the dorsal aspect of one of the fingers, abnormal redness will very speedily be produced, which in the first instance disappears completely on pressure; but, if the mustard has been kept on long enough, can be only imperfectly dispelled; and if the application be still longer continued, vesication will be the result. I had lately the opportunity of examining the brain of a man who had died of tetanus, complicated with incipient meningitis; the *post mortem* appearance of the latter being maculiform congestion of the pia mater. Having stripped off a portion of the affected membrane, and carefully washed away with a camel's-hair brush the cerebral substance adhering to it, I applied the microscope to one of the affected spots, and found that all the minute vessels were filled with crimson blood, while those of the surrounding parts were comparatively pale. It was evident that the red corpuscles were, in the former, so closely crammed together as to produce the appearance of a uniform mass, while in the latter they were present only in their usual proportion to the liquor sanguinis. Thus it appears that in the human subject, inflammation, whether induced by mechanical irritation or by an acrid application such as mustard, or of spontaneous origin, is characterized at an early period by a certain amount of obstruction to the progress of the blood through the minute vessels; a phenomenon, which it is therefore of great importance to understand.

It fortunately happens, that we have, in the transparent web of the frog's foot, an opportunity of observing with the utmost facility the circulation of the blood in the living animal, and of watching the effects produced upon it by irritating causes. It may naturally appear very doubtful whether observations made upon creatures so low in the animal kingdom as the Amphibia, can with propriety be brought to bear upon human pathology. A few facts will, however, suffice to show that no such doubts need be entertained. If a portion of moistened mustard be placed upon the web of a frog, tied out under the microscope, the blood-vessels will soon be found abnormally red; and if the application be continued long enough, all the capillaries will become choked with corpuscles so closely packed as to present the appearance of a uniform crimson mass; and by and by the epidermis will be found raised in the form of a blister over the part on which the mustard lay. These effects are precisely similar to those which we have seen to be produced by it upon the human skin; and before effusion has taken place, the vessels of the affected part exactly resemble those of the congested spot of inflamed pia mater above described. Again, if dry heat be made to act upon a part of the frog's foot,

there will result, in proportion to the elevation of the temperature and the duration of its action, undue redness of the vessels from accumulation of the blood-corpuscles; and if the burn have been sufficiently severe, vesication will soon take place as in the human subject. These and other similar cases indicate that the early stages of inflammation are alike in man and in the frog, and this conclusion is fully confirmed by examination of the bat's wing, which furnishes the means of watching the effects of irritants upon mammalian circulation. The very small size of the blood-corpuscles, and some other circumstances, render that animal much less suitable for the investigation than the frog; but with the use of high powers of the microscope and a little pains, the same sort of experiments can be made with both: and the careful observations of Messrs. PAGET and WHARTON JONES, and, I may add, also my own more limited experience with the bat, have shown that in all the details that can be observed, a complete similarity obtains between the effects of irritation upon the circulation in the two creatures. We may therefore rest fully satisfied that conclusions arrived at from the study of the early stages of inflammation in the foot of the frog will apply in all strictness to the same morbid process in man.

It is well known that the field of observation thus afforded has not been allowed to remain uncultivated. Since the microscope has been brought to its present state of perfection, not to speak of a previous period, men of established scientific reputation have devoted much patient labour to it; and any one who now enters upon this inquiry has the great advantage of possessing faithful records of accurate observations made by many able predecessors. But the number and discordance of the views entertained by different authorities regarding the cause of the "stasis" of the blood in inflammation, are sufficient evidence either that the subject demands further investigation, or else that it lies beyond the reach of human means of research.

Having been called upon in the capacity of a teacher of surgery to attempt an explanation of the matter to others, I felt bound to do my best, by personal observation, to form a judgement for myself; and several new facts which I have unexpectedly met with appear to throw such fresh and clear light upon the nature of disease, that I venture to submit them to the Royal Society.

#### SECTION I.

##### *On the Aggregation of the Corpuscles of the Blood.*

The tendency of the corpuscles of the blood to aggregate together, constitutes, as we shall see, an important element in the cause of the obstruction which they experience in the vessels of an inflamed part. It is therefore desirable that we should be acquainted with the nature of the phenomenon.

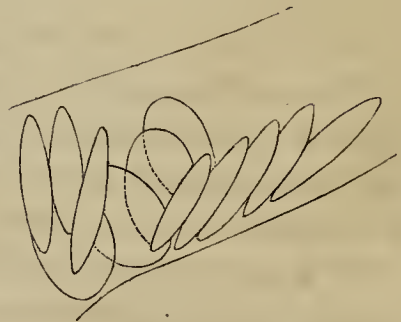
If a drop of human blood just shed is placed between two plates of glass and examined with the microscope, the red corpuscles are seen to become applied to one another by their flat surfaces, so as to form long cylindrical masses like piles of money, as first observed in 1827 by my father and Dr. HODGKIN; and the terminal corpuscles of



each "rouleau" adhering to other rouleaux, a network is produced with intervals of colourless liquor sanguinis. Rapid movement of the blood prevents this occurrence, but it commences as soon as the corpuscles approach to a state of quiescence, and I have seen short rouleaux already present in a drop drawn from my own finger within ten seconds of its emission. In this respect the aggregation of the red corpuscles differs from the coagulation of the fibrine, which does not begin till some minutes after withdrawal from the vessels. There is, in fact, no connexion whatever between the two processes, as is clear from the circumstance that if a drop of blood is stirred with a needle while coagulation is taking place, so as to remove the whole of the fibrine, the corpuscles, which have been separated from one another by the agitation to which they have been subjected, aggregate again in the serum in the same manner as they did at first in the liquor sanguinis. The beautifully regular form of the long masses of corpuscles has suggested to some persons the idea of the operation of some peculiar vital attraction in their formation, while by others the aggregation has been supposed due to merely physical causes, but has never, I think, received a complete explanation. For my own part, I am satisfied that the rouleaux are simply the result of the biconcave form of the red discs, together with a certain, though not very great degree of adhesiveness, which retains them pretty firmly attached together when in the position most favourable for its operation, namely, when the margins of their concave surfaces are applied accurately together, but allows them to slip upon one another when in any other position. There is never to be seen anything indicating the existence of an attractive force drawing the corpuscles towards each other: they merely stick together when brought into contact by accidental causes. Their adhesiveness does not affect themselves alone, but other substances also, as may be seen when blood is in motion in an extremely thin film between two plates of glass, when they may be observed sticking for a longer or shorter time to one of the surfaces of the glass, each one dragging behind it a short tail-like process; and as the movement of the blood diminishes so as to permit the formation of rouleaux, the latter may be not unfrequently seen adhering in the same way by one of their terminal corpuscles, as represented in the accompanying diagram.



That the cylindrical character of the aggregated masses is an accidental result of the shape of the blood-discs, is evident from the fact, that in the frog, although the same tendency to agglutination of the corpuscles exists as in Mammalia, yet, as their biconvex form renders it mechanically impossible for them to be applied to one another throughout their entire circumference, they become arranged in groups of an irregular form, as is shown in the annexed sketch of blood contained in a small vein of the frog's web.



Again, different specimens of mammalian blood differ very much in the amount of adhesiveness of their corpuscles; and when this property exists beyond a certain degree,

the discs stick together by any parts that happen to come first in contact, and retain that position more or less, so that the result is the formation, not of rouleaux, but of irregular confused masses. The most striking example which I have seen of this was presented by the blood of a bat, which had lived some days after having been severely wounded. In that case, chains of red discs might be seen adhering firmly by their edges, notwithstanding considerable force of traction operating upon them, and before they at last gave way, tail-like processes of considerable length were drawn out between every pair of corpuscles, indicating that they were very adhesive. These facts seem sufficient proof of the correctness of the view above expressed regarding the cause of the rouleaux.

The adhesiveness of the red corpuscles does not appear to be a vital property. When the fibrine has been removed from a drop of blood during the progress of coagulation, the rouleaux will form again, after being broken up, as many times as the experiment is repeated, until the blood becomes thick from dryness; and if evaporation be prevented by Canada balsam placed round the plate of thin glass, with suitable precaution against the approximation of the two plates, the rouleaux will remain perfect for several days (*e. g.* fourteen in one experiment of the kind), after which the very slow chemical action of the balsam upon the blood gradually renders it confusedly red and opaque. Gum mixed with blood seems to preserve it, like a pickle, from decomposition for a very considerable period; and if a piece of wet lint be suspended above such a specimen so as to prevent evaporation, the corpuscles will retain their adhesiveness for a long time (*e. g.* twenty-four days in one instance), until the water communicated to the mixture by the artificially damp atmosphere gradually renders them non-adhesive. These experiments were made in winter, when the low temperature prevents rapid decomposition; but it appears unlikely that even at that period of the year a part of the human body should retain any vital properties after having been left three and a half weeks mixed with strong gum, which, it is to be observed, alters very much the form and appearance of the corpuscles.

Both in man and in the frog the white corpuscles also are found aggregated together more or less in a drop of blood examined microscopically, and indeed they adhere much more closely than the red ones both to the glass and to one another; but as they are not disc-shaped, but globular, they do not become grouped into rouleaux, but into irregular masses, which, in consequence of their colourless and transparent character, are apt to pass unnoticed, or to be mistaken for masses of coagulated fibrine. If a portion of blood be allowed to run in between two plates of glass nearly in contact with one another, the white corpuscles will be found sticking together near the edge of the glass at which the blood entered, the blood having been as it were filtered of white corpuscles as it passed on; and this is not due to the greater size of the colourless corpuscles than the red, for I have seen it occur with frog's blood when there was room enough between the plates for the red corpuscles to lie edgewise, their transverse dimensions being greater than the diameter of a white corpuscle.



The red corpuscles also often adhere to the colourless ones.

It will be seen hereafter that the corpuscles of blood within the vessels of the living body present great varieties of adhesiveness, according to the amount of irritation to which a part may be subjected; such variations are also met with in blood outside the body, in consequence of differences in the quality of the plasma.

If a drop of very thick solution of gum-arabic, freshly prepared and free from acidity, be added to about four drops of blood, the red corpuscles of the mixture will be found to aggregate much more speedily and more closely than those of ordinary blood, a fact ascertained some years ago by Mr. WHARTON JONES and some other observers\*. The result is the formation of dense orange masses with large colourless interspaces, but without much regular appearance of rouleaux. On closely examining such a specimen, the red discs are seen to be much diminished in breadth and increased in thickness, and exhibit an extreme degree of adhesiveness, sticking together indifferently by their edges, or any other parts that happen to come first; and if one of the masses be stretched so as to break, the separating corpuscles become drawn out into long viscid processes, which at length give way in the middle, and each half is drawn into its respective corpuscle.

This remarkable effect cannot be accounted for by the mere viscosity of the plasma, which would not make the corpuscles adhere to each other more intimately than usual, unless they had themselves experienced some change, of which, indeed, their altered form is conclusive evidence. Further, if a very small quantity of acetic acid be added to the gum before mixing it with the blood, the corpuscles will be found to have lost altogether their adhesive character, although the mixture may be made viscid to any degree that may be desired. A little acid perspiration on the finger appears to prevent entirely the formation of rouleaux in a drop of blood taken from it; but after the finger has been washed, the usual appearances present themselves when more blood is drawn. Diminished adhesiveness of the red corpuscles is also the earliest evidence of the chemical action of tincture of cantharides and croton oil on the blood of the frog. A similar effect is produced when a drop of human blood is shed into a little fresh almond or olive oil on a plate of glass, and stirred slightly so as to break up the blood into minute drops. On microscopic examination of such a mixture, one sees the red discs aggregated as usual in the interior of the larger drops; but at their exterior, which is in contact with the oil, and throughout the smaller drops, the corpuscles are somewhat altered in form, being of less diameter, but thicker, though still in the form of discs, and at the same time they are found to have lost every trace of a tendency to adhere together; and when present in a thin layer of blood they stand apart at equal distances from one another, as if exercising a mutual repulsion, at the same time exhibiting molecular movements. If a drop of blood freshly shed upon a glass plate be stirred with a needle in an atmosphere of chloroform vapour, the rouleaux will be found to form less perfectly in proportion to the time that the chloroform has acted, until, if the period be as long as

\* Guy's Hospital Reports, vol. viii. p. 73.



thirty seconds, the corpuscles will be all cup-shaped, and will exhibit no disposition to aggregate. But no effect is produced on the formation of the rouleaux by stirring a drop of blood in the same way for a much longer time in an atmosphere free from chloroform. The aggregation of the corpuscles is not prevented merely by their becoming cup-shaped, and therefore unable to apply themselves to each other as usual. For the vapour of caustic ammonia, while it renders the corpuscles cup-shaped, seems rather to increase than to diminish their adhesiveness and aggregating tendency, and a temperature of about  $32^{\circ}$  FAHR. has similar effects with the alkali\*. Even in the mixture of blood and gum many of the corpuscles are cup-shaped, though adhering together with peculiar tenacity.

Whether or not it will ever be possible to explain these curious facts upon chemical principles seems very doubtful; but in the meantime, what appears most striking about them, and what most concerns the present inquiry, is that great effects may be produced upon the adhesiveness of the red corpuscles, both in the way of increase and diminution, by very slight changes in the chemical qualities of the plasma.

The galvanic current produces no effect upon the aggregation of the red corpuscles, either of man or of the frog, as I have ascertained by placing the fine platinum wire extremities of the poles of a powerful battery a short distance from one another between two slips of glass beneath the microscope, then completing the circuit by shedding a drop of blood between the plates, and immediately observing the result. In several such experiments I invariably found that aggregation took place as usual, and the only effect produced by the galvanism was a chemical change in the blood, dependent on electrolysis, gradually developing itself in the immediate vicinity of the poles, and causing solution of the corpuscles.

\* Since this paper was read, I was told by a gentleman well known in the scientific world, that he had observed, many years ago, that if blood was shed upon a plate of glass previously heated to the temperature of  $100^{\circ}$  FAHR., the red corpuscles showed no disposition to aggregation till the glass cooled, when the blood became killed, as he supposed, by the unnaturally low temperature. This appeared to me entirely irreconcilable with the fact, that in the frog the red corpuscles aggregate immediately after the blood has been shed, although there is no material difference between the temperature of the air and that of the body of the animal. But, if true, it would have important bearings, to which I need not here allude, upon the essential nature of inflammation. I have therefore thought it well to make some experiments upon the point. The plate of glass upon which the blood was to be placed was warmed by immersion in water of a known temperature, and quickly but carefully dried. A drop of blood from my own finger was then at once shed upon it, and without loss of time covered with a piece of thin glass, which had been kept warm by being laid upon a metallic plate of the same temperature as the water. By proceeding in this way, I was able to make observations upon the blood very soon after it had been shed; and when the glass was about  $100^{\circ}$  FAHR., the aggregating tendency was found just the same as in ordinary cases, and I detected short rouleaux already formed within five or six seconds of the escape of the blood from the vessels of the finger. The same state of things continued when the water was as high as  $136^{\circ}$ ; but when its temperature was carried up to  $155^{\circ}$ , the red corpuscles lost their disc-shape and some of them appeared to become broken up, and no rouleaux were formed either while the blood remained warm or after it had cooled. From these results, it is evident that heat does not interfere at all with the aggregating tendency of the corpuscles, unless it is sufficiently great to act upon them chemically.

The buffy coat in inflammatory blood was first explained by Mr. WHARTON JONES\*, who showed that it resulted from the red corpuscles aggregating more closely than usual, and therefore falling more rapidly through the lighter plasma, so as to leave the upper portions completely before the occurrence of coagulation. It was supposed by the same authority that this peculiarity of the red discs was due to increased fibrine in solution, rendering the liquor sanguinis abnormally viscid, and so operating like the admixture of gum above alluded to. But the fact that the corpuscles aggregate as closely after the fibrine has been removed as before, appears quite opposed to such a view. I have examined many drops of my own blood, before and after the removal of its fibrine, with the special object of ascertaining this point, and have never been able to detect any material difference between the aggregation in the two sets of cases. In the blood of the bat before mentioned, which was probably suffering constitutionally from inflammation, the corpuscles continued to retain their excessive adhesiveness for a whole hour after coagulation of the fibrine. I once made a similar observation on a specimen of horse's blood †, which, as is well known, presents the buffy coat in the state of health. Having divided the clot vertically several hours after coagulation had occurred, my attention was attracted, on looking at the section, by minute red points, like grains of sand, lying in the lower part of the buff, just above the coloured portion of the coagulum. On microscopic examination of a small piece containing some of them, they proved, as I expected, to be masses of aggregated red corpuscles, but with the peculiarity of being compact and globular instead of presenting the usual appearance of a network of rouleaux, and it was evident that the corpuscles had been excessively adhesive at the time when aggregation took place. Some of the red discs were now squeezed out from the fibrinous mass in which they lay, and as they escaped into the surrounding serum they at once adhered firmly in that fluid, forming again compact globular masses, such as, if in freshly-drawn blood, would necessarily give rise to the buffy coat; so that their adhesiveness seemed to have been in no way affected by the withdrawal of the fibrine from solution. It may of course be urged, that the fibrine, when in solution, may have impressed upon the corpuscles an adhesiveness which they retained after soaking for hours in serum, but this seems a very unlikely hypothesis. I suspect, therefore, that the peculiarities of the corpuscles of inflammatory blood are the result of other changes than the excess of fibrine.

From the facts detailed in this section, it appears that the aggregation of the corpuscles of blood removed from the body depends on their possessing a certain degree of mutual adhesiveness, which is much greater in the colourless globules than in the red discs; and that, in the latter, this property, though apparently not depending upon vitality, is capable of remarkable variations in consequence of very slight chemical changes in the liquor sanguinis.

\* British and Foreign Medical Review, October, 1842.

† This observation was made subsequently to the reading of the paper, viz. in November, 1857.



## SECTION II.

*On the Structure and Functions of the Blood-vessels.*

An acquaintance with the anatomy and physiology of the vascular system is indispensable to a successful study of the deviations from health exhibited in the circulation of the blood through the vessels of an inflamed part; it is not, however, intended to give here a full account of the subject, but merely to dwell upon some important points on which differences of opinion prevail.

It has long been a debated question whether or not the capillaries possess contractility, and there is still some difference of opinion among authorities upon the subject. With a view to throwing light upon this important point, I investigated carefully the structure of the minute vessels of the frog's foot; dissecting them out from between the layers of skin composing the web, so as to render their constituent material capable of clear definition with the microscope. The chief results have been communicated to the Royal Society of Edinburgh, in a paper that will shortly appear in their Transactions, "On the Structure of Involuntary Muscular Fibre\*." I need therefore merely repeat here, that while the capillaries were proved to consist, as has been long known, merely of a delicate homogeneous membrane beset with occasional nuclei, the minute arteries, some of them even less in calibre than average capillaries, were found to possess three distinct coats, namely, an external layer of cellular tissue, in variable quantity, longitudinally arranged, an internal extremely delicate lining membrane, and an intermediate circular coat, which constituted the principal bulk of the vascular parietes, and which, when highly magnified, was found to consist of a single layer of muscular fibre-cells, each wound spirally round the internal membrane so as to encircle it from one and a half to two and a half times.

Now when we consider the properties of muscular fibre-cells, which, as is shown in the paper referred to, are capable of contracting in the pig's intestine as much as to one-tenth of their length, it is impossible to conceive a more efficient mechanism for the constriction of a tube than is provided in these minute arteries. On the other hand, the capillaries are totally destitute of any structure known to be contractile. The changes of calibre which occur in the vessels of the living web are in perfect harmony with this anatomical description; for while the arteries, even to their smallest branches, are sometimes constricted to absolute closure, and at other times widely dilated, the capillaries are never found to be entirely closed, nor to present any variations in diameter, which are not explicable by elasticity of their parietes†.

The sketch at the top of the next page represents the calibre of an artery dividing into minute branches, with the capillaries into which they poured their blood. At the time when it was drawn, the artery and its branches were in a state of spontaneous

\* Transactions of the Royal Society of Edinburgh, vol. xxi. pt. 4.

† In this respect I merely confirm the observations long since made by Messrs. PAGET and WHARTON JONES.

contraction, yet the capillaries retained their full average dimensions. After a while the artery became so much more contracted as only to admit single corpuscles even through the main trunk; yet still the capillaries fed by it did not appear affected in calibre. This is but one example of what I have observed times without number.



The capillaries, though not contractile, are highly elastic, and by virtue of this property are capable of considerable variation in capacity, according to the distending force of the current of blood. Figs. 3 and 4 of Plate XLVII., traced with the camera lucida, show, besides the pigment in two chromatophorous cells of the frog's foot, part of a capillary in nearly extreme conditions in point of calibre. In fig. 3 the vessel is about equal in diameter to the length of a red corpuscle, while in fig. 4 it is so narrow that the corpuscles in it are pinched transversely and elongated. When the capillaries are most distended, their parietes are much thinner than when shrunk to their smallest dimensions; an estimate may be formed of the difference by comparing the close proximity of the corpuscles to the outer bounding line of the vessel in fig. 3 with the considerable interval in fig. 4, that interval representing the apparent thickness of the wall of the vessel. It is to be observed that the frog had been killed in a manner involving considerable hemorrhage before fig. 4 was traced, so that the capillaries were then little, if at all, distended with blood. The thinness of the walls of the capillaries, as compared with the small arteries, is, doubtless, calculated to favour the mutual interchanges which must take place between the blood in them and the tissues in their vicinity.

It is believed by some eminent authorities that mutual attractions and repulsions subsisting between the nutrient fluid and the tissues among which it flows, become a source of movement in the blood and assist its flow through the capillaries; while others regard the heart as the sole cause of the circulation: and the difference of opinion on this fundamental point in physiology involves discordance in pathological theory, for some who hold the former view consider the changes which occur in the circulation at the commencement of inflammation, to be principally owing to modifications of the 'vital' moving force\*. The view that such a cause of movement exists, has been supported partly by argument drawn from the phenomena of inflammation: but these, as we shall

\* See 'Outlines of Pathology and Practice of Medicine,' by W. P. ALISON, M.D., F.R.S.E., &c. 1844, pp. 115 *et seq.*



see, require a very different interpretation. It has also been based upon a supposed analogy between the circulation of the blood in the higher animals and certain movements observed to occur without any visible source of mechanical power in tubes and cells in the vegetable kingdom, and, as was thought, also in some of the lower forms of animal life: but though a resemblance may probably exist between some of these and the movements occurring in the processes of secretion and absorption and the circulation of nutrient fluid among the tissues of intercapillary spaces and non-vascular parts, the progress of modern discovery tends to show that the comparison is altogether inapplicable to the sanguiferous system. It would, I think, be out of place to enter fully into this discussion on the present occasion, but my own experience with the frog leaves no doubt in my mind that in that animal contractions of the heart are the only cause of the circulation. I will content myself with mentioning two observations bearing upon this question. The first of these has reference to certain movements which occur for a considerable time after cessation of the heart's action, and which, though of trivial and uncertain character, have had much stress laid upon them in this discussion. I have ascertained by observations made in several different cases, that they are produced by occasional spontaneous contractions and relaxations of the arteries. These changes in the calibre of the vessels continue, even in an amputated limb, for days after severance from the body\*: I have repeatedly watched them taking place, and seen them give rise to the movement of the blood.

The other fact to which I will allude, appears to me to decide of itself the question at issue. Having occasion to examine, under chloroform, some very small frogs, measuring about an inch from the tip of the nose to the end of the coccyx, I found that the blood in the capillaries invariably flowed in a stream pulsating synchronously with the beats of the heart, which were visible through the parietes of the thorax; and however mildly the anæsthetic was administered, the motion was commonly exceedingly slight between the pulses. Not unfrequently, although the arteries remained of full size, the blood moved in jerks, with considerable intervals of absolute stillness between the successive impulses which the contractions of the heart occasioned; yet no accumulation of corpuscles was produced in the capillaries, however long the animal was kept under observation. Had any other cause of motion than the action of the heart operated upon the blood, there must have been a continuous flow, however much accelerated at each pulse; for I must add, that there was nothing whatever of recoil after each onward movement, nor anything indicating obstruction to the progress of the blood.

Thus in these cases of intermitting capillary flow, it was matter of direct observation that the heart was the sole cause of the blood's motion; and as we know that in an animal under the influence of chloroform the changes of the blood from arterial to venous, and *vice versâ*, continue to occur in the systemic and pulmonary capillaries, and as we have every reason to believe that the processes of nutrition in the different parts

\* See the preceding paper on the parts of the Nervous System which regulate the contractions of the arteries, p. 618.

of the body go on then as usual, these cases appear to prove absolutely that the forces which are concerned in the mutual interchanges between the tissues and the nutrient fluid do not cause any movement whatever.

But even supposing that it were admitted, for the sake of argument, that the vital affinities do, under ordinary circumstances, cause some movement of the blood, but lose that power in an animal under chloroform, such an admission would hardly affect the discussion regarding the cause of stagnation in inflammation; for in a frog fully under the influence of the anæsthetic, in which, as we have seen, the heart is the only cause of circulation, all the phenomena that result from irritation of the web take place precisely in the same manner as in one to which the narcotic has not been administered. The fact that the heart, even though much enfeebled by chloroform, is capable, unaided by any other force, of maintaining the circulation for an indefinite period without the occurrence of obstruction in the capillaries, or any undue accumulation of corpuscles in them, affords positive proof that any other cause of movement which may be conceived to exist when chloroform has not been given, must be altogether insignificant, and that the cessation of its operation does not give rise to stagnation of the blood\*.

The veins of the frog's web afford very little evidence of contractility; but a small amount of unstriped muscular tissue, transversely arranged, is distinctly to be seen in the larger venous branches; and on one occasion I observed a very considerable degree of local contraction, as measured from the outer borders of the external coat of a vein running through a small area which I had pinched forcibly with forceps. I have also seen one expand on sudden dilatation of the arteries of the web, so that its diameter increased from twelve to fourteen degrees of a micrometer; but this is perhaps explicable by elasticity†.

It has been already mentioned that the arteries undergo spontaneous variations of calibre. Such changes are constantly going on at varying intervals, there being nothing of a rhythmical character about them. A struggle on the part of the animal is

\* Dr. SHARPEY has for many years alluded in his lectures to the circumstance that, the weaker the animal, the more do the effects of the successive cardiac impulses show themselves in the capillaries of the webs, as evidence that the action of the heart is sufficient to account for the circulation. He also informs me that he has frequently verified the observation of SPALLANZANI, that in the gills of the tadpole the flow of the blood ceases completely in the intervals between the pulses produced by the ventricular contractions.

† Since the reading of this paper I have noticed striking examples of the contractility of the larger veins in the higher animals. Thus, on exposing the jugular in a living calf, I have seen a particular part of the vessel irritated by the process of dissection shrunk to about a third of its previous calibre. In the human subject, too, when amputating lately at the shoulder-joint on account of contusion inflicted by machinery upon a previously healthy limb, I noticed the axillary vein reduced to about half its natural calibre at the part where it was divided, which was in the immediate vicinity of the injury. I have also had occasion to observe the *post-mortem* contractions of the subcutaneous veins of the sheep's foot, which are carried to such an extent as to reduce the vessels from the size of a crowquill to about that of a darning-needle. The minute veins also sometimes exhibit great contractility in the higher animals, as in the irregular constrictions often seen in those of the mesentery of the mouse, and in the remarkable rhythmical variations in calibre discovered by Mr. WHARTON JONES in those of the bat's wing (Philosophical Transactions, 1852).



generally accompanied by a very considerable constriction of the arteries, and sometimes by absolute closure of them. The contraction usually begins a very short time before the motions of the body, so that the struggle can commonly be predicted by the appearance of the vessels; and dilatation occurs when the creature becomes quiet. Hence the changes of calibre are evidently under the control of the nerves. An account of an inquiry into the parts of the nervous system by which this control is exercised, will be found at p. 607 of this volume; and from the experiments there recorded, it will be seen that either extreme constriction or full dilatation of the arteries of the web may be induced at pleasure, by operating upon the spinal cord. A very good opportunity is thus afforded for studying the effects produced upon the capillary circulation by changes of calibre in the arteries, without employing any means acting directly upon the foot. This is a matter of very great importance, for applications made to the web for the purpose of inducing alterations in the dimensions of the vessels, give rise at the same time to other consequences of irritation, which complicate such experiments in a most deceptive manner, so as to have misled, as I believe, some of the best observers who have devoted attention to this subject.

The following account embodies the results of numerous observations in which this source of fallacy was carefully avoided, the variations in the calibre of the vessels being generally either induced by operations on the cord, or else such as occurred spontaneously.

In a perfectly healthy state of the web with the heart beating powerfully, when the arteries are of about medium width, the current of blood in them is so rapid that the individual corpuscles cannot be discerned; but in the capillaries, whose aggregate calibre is very much greater than that of the arterial trunk which feeds them, the flow is so much slower that they can be pretty clearly distinguished. When the arteries are fully dilated, if the heart continues to act with the same energy, the blood appears to move as rapidly in them as before, though of course in much larger quantity; while in the capillaries the flow is extremely accelerated, so that it becomes as impossible to see the blood-corpuscles in them as in the arteries. On the other hand, when the arteries are considerably constricted, the blood moves more slowly through the capillaries than when the tubes of supply are of medium size, and at the same time the narrowed arteries appear to filter the blood more or less of corpuscles, which are found in smaller numbers in proportion to the liquor sanguinis in the capillaries: and if the constriction of the arteries is sufficiently great, the web is rendered quite pale in consequence of the small number of corpuscles in it, which nevertheless continue to move among the tortuous capillaries, producing in the field of the microscope an appearance something like that of a few flies playing about in a room. Finally, if the arteries are completely constricted, all appearance of flow in the capillaries vanishes, and the web has a wholly exsanguine aspect. Under these circumstances, even the veins, though still of large calibre, may contain little besides colourless liquor sanguinis, which has continued to ooze through the contracted arteries when the corpuscles have been completely arrested; and so incon-

spicuous do the veins become in consequence of this change in the quality of their contents, that it may be extremely difficult to distinguish them from other tissues; the appearance of the web on superficial observation being as if it possessed no blood-vessels at all. This remarkable condition, which, so far as I know, has not been before described, may last for several minutes in consequence of irritation of the cord, and in one case I observed it occur spontaneously, and continue for five minutes together. It appears to be comparable to the dead whiteness of the human fingers when benumbed with cold, or the perfect pallor of the cheek in faintness; while blushing is no doubt caused by full dilatation of the arteries.

Such, according to my experience, are the effects produced upon the circulation by changes of calibre in the vessels of a perfectly healthy web. The arteries regulate by their contractility the amount of blood transmitted in a given time through the capillaries, but neither full dilatation, extreme constriction, nor any intermediate state of the former is capable *per se* of producing accumulation of corpuscles in the latter.

### SECTION III.

#### *On the Effects of Irritants upon the Circulation.*

It is well known that the application of an irritant substance to the web of the frog's foot is followed by changes of calibre in the blood-vessels, and also by an abnormal accumulation within them of the corpuscular elements of the blood. The first experiments which I performed upon the frog were directed to the solution of the much-debated question, whether or no the latter were a mere consequence of the former; and although it has, I think, been sufficiently shown at the conclusion of the last section that such cannot be the case, yet it will be well to allude shortly to these experiments on account of their further bearing upon the subject of this inquiry.

It occurred to me, that if, instead of the powerful irritants commonly used in these investigations, some exceedingly mild stimulant were employed, the changes in the calibre of the vessels might perhaps be produced without concomitant alterations of the blood. The material which appeared most suitable for this purpose was warm water, which is known to cause, in the human subject, increased redness without inflammation of the part to which it is applied.

Accordingly, in September 1855 I endeavoured to ascertain its effects upon the frog. In most of the experiments, the foot of the animal being stretched under the microscope upon a glass plate somewhat inclined, so that any fluid upon it might run off quickly, an assistant threw a stream of water of known temperature upon it by means of a syringe, the eye of the observer being kept over the microscope, which was provided with a micrometer in its eyepiece. In this way the effects produced by the water could be seen almost immediately after it had ceased to play upon the web, and the changes of calibre in any artery selected for observation were noted with precision. It was found that the result of the warm application was constriction of the arteries to absolute



closure, generally lasting for several seconds\*, and then giving place to dilatation beyond their original dimensions, to which they afterwards gradually returned. The dilatation differed in different instances, being generally more decided and more permanent when the water was hotter and longer applied†. In one case, water at 100° thrown upon the web for a brief period caused constriction for a few seconds in the artery under observation, followed by dilatation. While the vessels were still above their usual calibre, more water of the same temperature was applied as before, and again induced contraction followed by abnormal dilatation, which was again made to give place to constriction by a third similar application: the experiments were repeated within a few seconds of each other.

When water not higher in temperature than from 110° to 140° was thrown for not longer than a second or two upon a perfectly healthy web, the changes above described in the diameter of the arteries produced effects upon the flow of blood through the capillaries, precisely similar to those mentioned at the conclusion of the last section. Thus in one such case the constriction of an artery lasted for several seconds, and was in the first instance so tight as to prevent any flow in the field of capillaries supplied by it; then relaxing slightly, it allowed single corpuscles to pass along it with great difficulty, so that the blood became almost entirely filtered of its particles, and at the same time the force of the heart being to a great extent taken off from the elastic capillaries, liquor sanguinis almost destitute of corpuscles flowed in slow pulsating streams along the veins: finally, the dilatation becoming complete, blood of ordinary appearance rushed through with great rapidity.

If, however, such experiments had been several times repeated upon the same foot, and more especially if the warm water had acted for longer periods, another class of symptoms began to show themselves; the corpuscles passing on less freely than the liquor sanguinis through the capillaries, and lagging behind so as to accumulate in abnormal proportion to the plasma, and stagnating completely when the force of the heart was partially taken off through contraction of the arteries, though passing on again when the vessels dilated‡.

\* The period of constriction varied much in different instances, and it sometimes passed off (if it occurred at all) before it could be observed. It was best marked in a case, in which, the animal being very quiet, chloroform was not employed. The anæsthetic appears to impair the functions of the spinal cord as a regulator of the calibre of the vessels; and its administration is generally followed by their dilatation.

† Water of the temperature of the room applied in the same way after warm water had been several times employed, caused complete constriction of the arteries, lasting for several seconds; but the subsequent dilatation was very little if at all beyond the normal calibre.

‡ This effect of arterial contraction in producing accumulation and stagnation of corpuscles in the capillaries has been described by Mr. WHARTON JONES as occurring in a state of health (*vide* Guy's Hospital Reports, *loc. cit.*). The reason of this I believe to have been, that much greater care than is generally supposed is required in order to avoid any irritation whatever of the delicate webs. The vicinity of the warm hand is particularly apt to produce this effect; and I have known it, when continued for a quarter of an hour, cause complete stagnation of the blood throughout the webs, while a very much shorter period is sufficient to induce a decidedly abnormal condition. I have myself only become fully aware of the great susceptibility of the foot of the frog to injury from warmth since the reading of this paper. An unhealthy

Thus in one case an artery under observation measuring  $2^{\circ}$  (degrees of the micrometer), the blood was flowing in all the capillaries supplied by it, though containing a very abnormal amount of corpuscles. After a few minutes, the vessel contracted spontaneously to  $1\frac{1}{4}^{\circ}$ , and though this was only about a medium width, the flow of the blood became much retarded in the capillaries, and in one of them ceased almost entirely. Water of  $115^{\circ}$  FAHR. being then thrown upon the web, the calibre of the artery was raised to above  $2^{\circ}$ , and the flow was resumed in all the capillaries. A few minutes later the vessel again contracted spontaneously to  $1\frac{1}{2}^{\circ}$ , when stagnation of the blood became nearly complete in a few of the capillaries. Water at  $120^{\circ}$  was then applied and caused constriction to a further degree, followed by dilatation to above  $2^{\circ}$ : during the constriction, the blood scarcely moved at all in the capillaries, but on the occurrence of the dilatation it again flowed in all of them.

If the applications were still further continued, the red discs became more and more closely packed, till at last they were crammed together so as to produce a uniform crimson mass, unaffected by the heart even in the widest state of the arteries.

It was perfectly clear that in these experiments the stagnation of the blood depended on something more than mere contraction of the arteries; and it also appeared impossible to account for it satisfactorily as a result of their dilatation. That inflammatory stasis might occur independently of alteration in the calibre of the vessels, was also shown by an experiment with capsicum made at this period. A morsel of this substance having been placed upon the middle of a web in which the circulation was going on in perfect health and with unusual rapidity, the effect was great accumulation of corpuscles in two or three capillaries for a very short distance round the spot where the capsicum lay, unaccompanied by any change in the vascular dimensions.

Chloroform proved to be an agent which very readily induced stagnation when locally applied; and when it was administered in the usual way by inhalation for the purpose of performing experiments with warm water, it was found necessary to protect the webs carefully from its vapour, which otherwise produced the same appearances of congestion as the hot application. In one instance in which a small quantity of the liquid had been applied to the web, I saw the red corpuscles adhering to one another by their flat surfaces, in a manner not seen in the healthy condition, and exactly as described by Mr. WHARTON JONES to take place after the application of a strong solution of salt; but from the very slight tendency of chloroform to mix with water, it was impossible to believe that it had operated by way of exosmose, as was supposed by the authority just named to be the case with the saline solution\*.

state of the webs is indicated to the naked eye by conspicuousness of the blood-vessels. In perfect health they are quite invisible without the microscope, and in all cases the appearance of any vessel as a distinct red streak is pretty sure indication of a certain amount of irritation.

\* It was believed that the solution of salt abstracted water from the blood as it flowed through the capillaries, and that the liquor sanguinis being consequently inspissated, the red corpuscles assumed an abnormal tendency to aggregate together (see Guy's Hospital Reports, *loc. cit.* p. 40). This view has been more recently



From the facts above mentioned, I became convinced that no satisfactory explanation had as yet been given of the obstruction experienced by the blood-corpuscles in the vessels of an inflamed part, and in September 1856 I again continued the investigation. Mustard being admitted to produce inflammation in any part of the human body to which it is applied, and also not appearing likely to act by way of exosmose, I selected it as a suitable irritant, and in order to study its effects accurately, placed a small portion of its moistened flour, about a line in diameter, upon the middle of the web of a large frog under chloroform. After a while, thinking that I saw stagnation in a capillary just at the margin of the mustard, I removed the latter with a camel's-hair brush, and was surprised to find that throughout the whole area on which it had lain, the capillaries were crammed with either stagnant or very slowly moving red corpuscles. The limits of the part so affected corresponded exactly with the extent of the application of the mustard, although the capillaries of adjoining parts were fed and drained by the same arteries and veins.

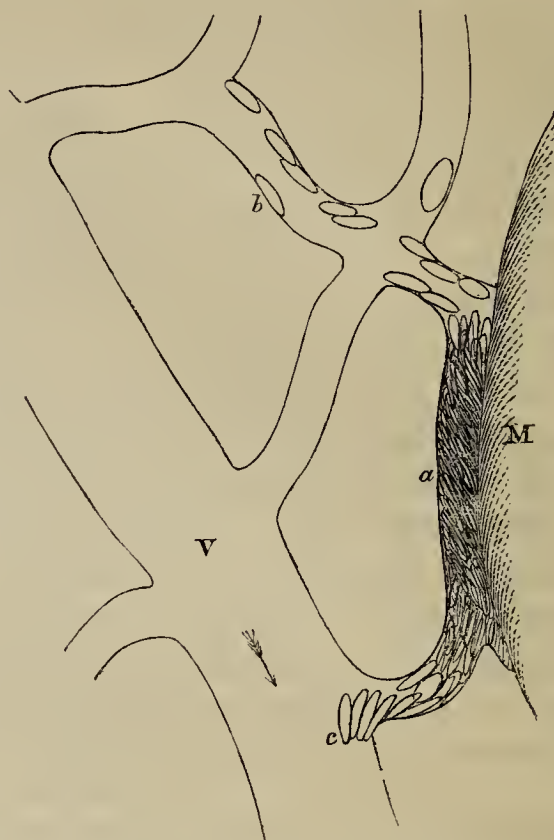
On the 3rd of October I made another similar experiment, selecting a part of the web where a considerable artery divided into small branches. Before applying the irritant, I had ascertained that the artery running through the area measured  $6\frac{1}{2}^{\circ}$  of an eyepiece micrometer\*, while a large vein near it had a diameter of  $12^{\circ}$ . About half a minute after the application of the mustard, when I first looked through the microscope, the arteries of the web generally were much dilated, and the flow, which had before been somewhat languid, was rapid in all its capillaries. The opacity of the mustard prevented the vessels beneath it from being observed, but at a short distance from its edge the artery measured  $10^{\circ}$  and the vein  $14^{\circ}$ . In a few minutes the capillaries seen beneath

advocated by a German writer, FR. SCHULER of Glarus (Würzburg Verhandlungen, 1854), with a very elaborate series of difficult experiments. One of these, however, seems almost conclusive against his theory. Having injected a solution of prussiate of potash into the veins of a frog, he applied sulphate of iron to the webs, but found that very little blue colour was produced *until the epidermis of the web was scraped away*, when it showed itself distinctly. Considering how delicate a test prussian blue is of the presence of a mixture of the two salts, this result seems to show that there is far from being the same tendency to mutual interchange between the blood in the capillaries and fluids in contact with the surface of the web, as there would be if the intervening material were dead animal membrane of the same tenuity. Were the disposition to exosmosis and endosmosis such as is assumed in the above explanation of stasis from a solution of salt, it would be impossible for the animal to live long either in water or on dry earth. In the former case the blood would soon become diluted from imbibition, and in the latter inspissated from evaporation. But it is well known that frogs will live for months in water without food, and I have kept them for weeks together upon dry earth at a temperature of about  $60^{\circ}$  FAHR., and on removing from the webs a layer of dust and exfoliated epidermis, found the circulation perfectly healthy. Since the reading of this paper, I have seen a remarkable example of the power of the tissues of the webs to resist imbibition of water in an amputated limb with the blood retained in the vessels by a ligature. Though it was kept in wet lint, the blood in the vessels showed no indication of admixture of water till the tenth day, and then only in those parts of the web in which the arteries and pigment-cells gave evidence that they had lost their vitality. For further particulars regarding this experiment see pages 618 and 640 of this volume.

\* The micrometer used on this occasion was differently graduated from that employed in the warm water experiments.

the extreme margin of the mustard, which was slightly transparent, were observed to be of crimson colour, in consequence of their containing closely-crammed corpuscles, some of which were still moving, while others were motionless. On the application of a higher power, the continuations of these capillaries immediately exterior to the mustard showed, many of them, red corpuscles sticking to their walls, and more or less obstructing the progress of the blood through them.

In the accompanying sketch of the vessels at one part, together with those corpuscles which were motionless in them, M represents the edge of the mustard, *a* a capillary partly overlaid by the mustard and crammed with stagnant corpuscles, *b* a capillary with red discs adhering to its internal surface, but still transmitting blood, while further from the mustard all the corpuscles were in motion, and consequently none appear in the drawing; *c* was a rouleau of red corpuscles projecting from a stagnant mass into the vein V, through which the blood was flowing rapidly; yet the rouleau, though its free end was moved to and fro by the current, was prevented by the mutual adhesiveness of its corpuscles from being broken up or detached. Thus it was evident that in the capillaries of the space covered by the mustard, the red corpuscles had an abnormal tendency to adhere



both to the walls of the vessels and to one another, and were on this account accumulating and sticking within them, while almost immediately outside the mustard, the blood in the capillaries presented the same appearance as in other parts of the web. This effect was independent of changes in the calibre of the vessels, for any results of alteration in the size of the artery under the mustard must have been shared by the surrounding capillaries, which also derived their blood chiefly from it; and that the vessel was dilated to the same degree there as elsewhere, was shown by the fact, that its branches continued throughout the experiment to transmit full streams of blood after emerging from beneath the opaque mass. I also measured some capillaries by micrometer before the application of the mustard, and again after it had caused stagnation in them, and found that their dimensions remained the same\*.

\* The increased pressure upon the blood in the capillaries, resulting from obstruction to the progress of the corpuscles, leads to the distension of their elastic parietes up to a certain point, but, generally speaking, not further. In the present case, before the application of the mustard, the web, irritated probably by the vapour of the chloroform, was affected with a slight congestive tendency, far short of that which induces stagnation, but yet sufficient to give rise to full distension of the capillaries. When the web has been perfectly healthy to begin with, I have seen a marked increase of calibre in the capillaries on the occurrence of



The precise limitation of the effect produced upon the blood in these two experiments to the area covered by the mustard, showed that it was the result of a direct action of the irritant either upon the blood that flowed beneath it, or upon the tissues of the part of the web on which it lay, the blood being in the latter case affected secondarily. I made several experiments to determine whether the adhesiveness of the corpuscles in blood out of the body was increased by contact with, or vicinity to mustard, placing minute portions of it between plates of glass, and shedding a drop of blood from a frog, so that it might run in between the plates, and watching the result. I could, however, detect no evidence of such change in the corpuscles as I was seeking; whence I inferred that the blood had been only affected secondarily to the tissues in the two mustard experiments.

A careful study of the effects produced by the local application of chloroform to the web, confirmed in every respect the conclusions previously arrived at. If, while the eye of the observer is over the microscope, a minute drop of this liquid is placed with a camel's-hair brush upon the part in the field of view, it evaporates in perhaps two or three seconds; and if the web be dry, the time of its disappearance can be distinctly seen. Yet though it has so short a time to act, it produces so powerful an effect upon the part, that the red corpuscles immediately experience obstruction to their progress, and move too slowly in abnormal numbers through the capillaries, which perhaps become entirely clogged with them; the arteries meanwhile being in the state best adapted for easy transmission of the blood, *i. e.* full dilatation. In one such experiment I saw a few corpuscles sticking together in a capillary and moving with difficulty, from evident tendency to adhere to its parietes, their number gradually becoming augmented by the adhesion of others that followed, till the mass grew so large as to fill the vessel for some distance, when it finally stopped. In another case, the circulation being perfectly natural in the web, and the corpuscles moving on at slight intervals with no tendency to adhere, on a drop of chloroform being applied, I saw the very same corpuscles instantly become checked in their progress by sticking to each other and to the capillary walls, and move on slowly in masses with considerable intervals. Thus the nature of the effect produced upon the red corpuscles of the blood when chloroform is applied to the web is the same as that caused by mustard, *viz.* an abnormal degree of adhesiveness; whereas the earliest evidence of the direct action of chloroform on blood out of the body is the loss of the adhesive property of the red discs, as has been mentioned in Section I.\* That the effect on the blood within the vessels of a part inflamed by chloroform is secondary to a change in the tissues is further proved by the circumstance, that abnormal accumulation of slowly moving corpuscles may last for hours together stagnation in them. This I noticed particularly in a case in which caustic ammonia was the irritant employed. I would remark, however, that the eye is apt to be much deceived on this point unless the micrometer is used. Those vessels which are crammed with corpuscles, being of dark crimson colour, look at first sight larger than others, really of the same size, which contain the normal proportion of liquor sanguinis, and are therefore of pale tint.

\* See p. 650.

without stagnation, as a consequence of the application of this irritant for an extremely brief period\*. Long after all the blood which could possibly have been directly acted on by the chloroform has left the vessels, successive fresh portions continue to experience precisely similar changes in passing through the irritated area.

Heat produces similar effects. If the foot of a frog which is under the influence of chloroform be covered entirely with wet lint, except a small area of one of the webs, and a red-hot cautery iron be held for a few seconds about half an inch above the exposed part, inflammation will be excited in the area in proportion to the time of the action of the dry heat upon it; but on removal of the lint, the circulation will be found perfectly healthy in the surrounding parts. In the severer cases stagnation is universal in the exposed area, and the epidermis becomes eventually raised by the exudation of serum beneath it; but in milder instances nothing more than accumulation of slowly-moving corpuscles is produced, and I have observed this state of the part to continue for hours after the heat was applied. Here again the effect on the blood was obviously not due to the direct action of the heat upon it, but to some changes which it had effected in the tissues of the part on which it had acted.

Evidence of the same kind, but still more conclusive, is derived from the effects of mechanical irritation, where the agency is free from all objection of possible chemical action on the blood. The method adopted was that of compressing a small part of the middle of the web between little pads of soft material attached to the ends of the blades of a pair of surgical dressing forceps, by which the degree of pressure could be regulated at will. The results of this treatment were identical with those of heat, as just described. If the pressure was not made too severe, no mechanical obstruction was produced in the vessels, which nevertheless became loaded with slowly-moving or stagnant corpuscles; and on one occasion I observed the capillaries of an area which had been pinched, still transmitting languid streams of blood containing great excess of corpuscles several days after the injury had been inflicted, while in the surrounding parts the circulation continued perfectly healthy. Mechanical violence, like heat, chloroform and mustard, had effected an alteration in the tissues on which it operated, in consequence of which the blood in their vicinity assumed abnormal characters; and many other facts of similar nature might be added, if necessary, to show that this is the course always followed when accumulation of corpuscles in the vessels is induced by the action of irritants.

In discussions regarding the causes of the phenomena of inflammation seen in the frog's web, the great difficulty has hitherto been to account for the puzzling fact, that while the arteries still retain that state of enlarged calibre which is best adapted for easy transmission of the blood, its accelerated movement comes to give place to unnatural

\* The gradual supervention of the effects of irritation upon the blood may be watched very conveniently by arranging a piece of lint soaked in chloroform, so that the vapour may play upon the web while the eye of the observer is over the microscope. If the chloroform be removed when the tendency to accumulation of corpuscles exists in a very slight degree, restoration to health will occur within a few minutes.



retardation and ultimate stagnation. Accordingly, various theories, mechanical, chemical and vital, have been proposed \* to explain the transition from "determination of blood," as the condition of dilatation of the arteries with increased flow through the capillaries has been termed, to inflammatory congestion, as the accumulation of corpuscles in the vessels may perhaps be most fitly designated. But the second simple experiment with mustard, to which I would again direct the attention of the reader, proves in a very beautiful manner that these two results of irritation are totally distinct in nature and independent in cause. The dilatation of the arteries, it will be remembered, affected not only the part on which the mustard lay, but also all the rest of the web, showing that it was developed indirectly through the medium of the nervous system; whereas the accumulation of the blood-corpuscles in the vessels below the mustard was, as we have seen, the result of the direct action of the irritant upon the tissues. The arterial dilatation in the web generally led to no changes in the quality of the blood, which, though the experiment was continued for some hours, retained to the last its natural characters, just as would have been the case had the enlargement of the vessels depended on an operation performed upon the spinal cord. The accumulation of corpuscles, on the other hand, implied an alteration in the properties of the blood, viz. an abnormal adhesiveness in the red discs. Determination of blood is thus a purely functional phenomenon, and, like a blush upon the cheek, becomes obliterated after death by the *post-mortem* contractions of the vessels: inflammatory congestion, on the contrary, is the first evidence of organic lesion, and declares itself as distinctly in the dead as in the living, being the most important if not the only sign of the early stages of inflammation discoverable on dissection†, as for instance in the case of incipient meningitis mentioned in the Introduction to this paper.

Although determination of blood, as met with in the frog, is thus entirely independent of inflammatory congestion, yet it is of great interest with reference to human inflammation. Dilatation of the arteries is now generally admitted to be the result of the relaxation of their muscular fibres; and that it is a purely passive phenomenon, seems to be absolutely demonstrated by the fact which I have pointed out elsewhere‡, that after the vessels have been liberated from the control of the nervous system by removal of the spinal cord, they dilate fully if the heart continues to act sufficiently

\* See 'Pathology and Practice of Medicine,' by W. P. ALISON, M.D., F.R.S.E.; 'Principles of Medicine,' by C. J. B. WILLIAMS, M.D., F.R.S.; 'Lectures on Surgical Pathology,' by JAMES PAGET, F.R.S.; 'Essay on the state of the Blood and the Blood-vessels in Inflammation,' by T. WHARTON JONES, F.R.S.; 'Guy's Hospital Reports,' vol. viii.; 'Clinical Lectures,' by J. H. BENNETT, M.D., F.R.S.E.; also Professor HENLE, as quoted by WHARTON JONES, *op. cit.*

† Since the reading of the paper, I have pointed out, that in consequence of the persistent fluidity of the blood which continues in the smaller vessels for days after death, the red corpuscles have time to gravitate into dependent parts, and thus give rise to that appearance of *post-mortem* congestion which more or less closely simulates to the naked eye what would have resulted from inflammation during life. See a paper by the author on spontaneous gangrene from arteritis, and the causes of coagulation of the blood in diseases of the blood-vessels, Edinb. Med. Journal, March 1858.

‡ See page 624 of this volume.

powerfully to distend them with blood, but not otherwise. Recent physiological discovery has shown that the arteries are not singular in being thrown into a state of muscular relaxation through irritation of the parts of the nervous system connected with them, the same being the case with the heart, the intestines, and apparently also with other hollow viscera. In a preliminary account of an inquiry into the functions of the visceral nerves, published in the 'Proceedings' of this Society\*, I have given some notice of experiments which seem to show that in the case of the viscera alluded to, the state of relaxation under such circumstances is the result of the more energetic operation of nerves, which, when working more mildly, increase the muscular action of the same organs; the functions of the ganglia specially concerned in regulating the movements of the viscera being exalted by gentle stimulation on the part of the afferent nerves connected with them, but depressed by stronger excitation. In that paper the opinion was expressed, that the same explanation probably applies to the relaxation of the arteries, in consequence of nervous irritation; the general impression conveyed by the experiments with warm water above related being that arterial contraction was most apt to show itself when the degree of irritation was least, while dilatation was most marked when the stimulus was strongest. I have lately seen a striking illustration of this principle in a very simple experiment, which I was induced to make in consequence of reading a paper recently published by a French author, M. J. MAREY†. If a blunt-pointed instrument, such as the end of a pair of dissecting forceps, is drawn with gentle pressure along the back of the hand while it is in a state of moderate redness, the blood being driven out of the vessels, a pale streak results, which immediately disappears, in consequence of the return of the blood into the part. In a few seconds, however, a pale stripe, towards a quarter of an inch in breadth, becomes developed at each side of the line along which the instrument passed, that line having now assumed a red colour, if the pressure employed was at all forcible. This is M. MAREY's experiment; and there can be no doubt that his interpretation of the secondary paleness is correct, viz. that it depends on reflex arterial contraction. The red line, when it occurs, is evidently due to the direct action of the pressure upon the tissues, being, as M. MAREY correctly states, exactly of the same breadth as the instrument used. But I find that if the pressure be made with considerably greater force, so as to be positively painful, while the first white streak appears as before in consequence of the blood being dispelled from the vessels, the secondary paleness does not occur, but, on the contrary, a patch of the adjacent skin, extending for perhaps half an inch on each side, assumes abnormal redness, which lasts for a longer time than the paleness to which the other experiment gives rise. Here, the irritation being severe, the blood vessels are thrown through the medium of the

\* Vol. ix. No. 32. The paper here referred to was written subsequently to the reading of the manuscript of this essay, and this was also the case with the remarks in the text on determination of blood.

† 'Recherches Hydrauliques sur la Circulation du Sang,' par M. J. MAREY. The separate copy of this paper, sent me by the author, does not contain any mention of the Journal in which it was published, so that I am unable to give proper reference to it.



nervous system into a state of muscular relaxation, instead of the contraction which is induced by a more gentle application of the same stimulus.

To return to the consideration of inflammatory congestion. Further light was thrown upon the condition of the blood in the vessels of an irritated part by a series of observations made when the circulation had been arrested by amputation of the limb, or by a ligature round the thigh. This field of inquiry was unexpectedly opened during the course of an experiment made with a view to ascertaining the effects produced by an irritant upon the pigmentary system independently of the circulation, as will be described in the next section. On the 13th of October 1856, a frog having been killed by destruction of the brain, the soft parts of one of the thighs were divided to the bone, and a small piece of mustard was placed on one of the webs of that foot. An hour afterwards, on removing the mustard, I saw to my great surprise that the small area on which it had lain was red to the naked eye, and that its capillaries, examined microscopically, contained abundance of closely-packed corpuscles, while in surrounding parts the blood was in the same condition as before the experiment, viz. of pretty healthy aspect. In other words, well-marked inflammatory congestion had been produced by the mustard, and I afterwards found that the same thing occurred in a limb completely severed from the body\*.

This fact of course completely eliminated variations in the calibre of the vessels and consequent changes in the circulation from among the causes of congestion, and demonstrated conclusively its independence of the central organs of the nervous system. Further, it presented a very good opportunity for studying the state of the blood in healthy and inflamed parts, unaccompanied by the effects of rapid movement. In subsequent similar experiments, it was found that the corpuscles were not brought to the irritated area by anything that indicated a mutual attraction between the former and the latter, but were simply carried along by slight accidental movements of the blood, such as are caused by *post-mortem* contractions of the arteries, and instead of moving with facility, as in other parts, stuck when they arrived in the vessels of the area, in consequence of undue adhesiveness. The accumulation of the corpuscles was never to such an extent as in cases in which the heart was driving the blood through the part, but it affected the arterial and venous branches as well as the capillaries. Thus, if a large vein happened to run through the spot upon which the mustard was placed, it became in time choked with a crimson mass of corpuscles in that part of its extent which lay beneath the mustard; but immediately beyond, in both directions, the blood in it contained no more than the usual proportion of corpuscles, or sometimes considerably less; and these moved freely to and fro when the web was touched, whereas those

\* Mr. PAGET, to whom I mentioned this experiment, has informed me that the fact that stasis may be induced by application of irritant substances to the frog's foot after the arrest of the circulation by ligature of the thigh, had been previously discovered by Dr. H. WEBER of Giessen (*MÜLLER's Archiv*, 1852), and that SCHULER of Glarus had afterwards ascertained that the same thing occurs in an amputated limb (*vide Würzburg Verhandlungen*, 1854).

within the area remained fixed. This proved that the cause of the accumulation of the corpuscles did not reside specially in the capillaries, and also showed distinctly that it could not be explained by mere abnormal adhesiveness of the vascular parietes, which was, I understand, the view entertained by the late Dr. MARSHALL HALL; for supposing the walls of the vessels to experience such a change, which seems by no means improbable, this could only lead to encrusting of the lining membrane of such a vein with adhering corpuscles, and not to the occupation of its whole calibre by them, as took place in these cases, unless the corpuscles were themselves also abnormally adhesive.

Another important fact which was brought out by this class of experiments is, that mere quiescence of the blood in the vessels of a healthy part fails to induce aggregation of the red corpuscles, such as occurs in blood outside the body. In the parts which had not been subjected to irritation, the corpuscles exhibited no trace of adhesiveness; and though completely at rest, they were nowhere to be seen grouped together, surface to surface, although in the larger vessels there was abundant space for the occurrence of this phenomenon, which invariably presents itself in freshly drawn frog's blood examined between plates of glass in a sufficiently thick film. On one occasion, when examining the tissues of the web of a frog under chloroform, the limb being kept steady by a string tied tightly round the thigh, so as completely to arrest the circulation, I was particularly struck with the total absence of adhesiveness in the red corpuscles; so much so, that, as the foot had been kept moist without circulation for about three hours, I suspected that it must have imbibed water, which, when mixed with blood outside the body, destroys altogether the adhesiveness of the red corpuscles. This, however, proved to be a mistake; for, having occasion to administer more chloroform, I applied it on a piece of lint of considerable size without taking the usual precaution of protecting the foot from the vapour, and left it so for about a quarter of an hour. On re-examination of the web, the red corpuscles were found to possess much mutual adhesiveness, and in the larger vessels were grouped together into masses, with considerable spaces of clear liquor sanguinis, just as in the best-marked forms of aggregation in frog's blood outside the body. One of these masses was drawn by camera lucida, and is represented in the sketch at page 648, along with the outline of the vessel in which it lay. I afterwards purposely induced a similar change in the blood within the vessels of an amputated limb by means of mustard\*. Having ascertained that the red corpuscles, though they had been long at rest, were perfectly free from the slightest tendency to aggregation, I suspended, at a little distance from the web, a piece of lint smeared with freshly prepared mustard, so that the pungent vapour of the volatile oil might play upon it; and left it so for about a quarter of an hour, when I found the red discs aggregated, as usually seen in frog's blood outside the body. I then shed some blood from the other leg between two plates of glass, and on carefully sketching and comparing the groups of corpuscles in this specimen and those within the vessels of the irritated webs, found that

\* This experiment was performed subsequently to the reading of the paper.



their characters were precisely similar\*. These are examples of what very numerous observations have tended to establish, namely, that on the one hand the red corpuscles in the vessels of a perfectly healthy part are free from adhesiveness; and on the other hand, the adhesiveness which they acquire in inflammatory congestion, though varying in proportion to the degree of irritation, is never greater than occurs in the blood of a healthy part when withdrawn from the body.

These conclusions, if correct, represent cardinal truths, both in physiology and pathology, implying relations of the tissues to the blood both in health and in disease, such as have never before been demonstrated, or, I believe, even suspected. I was therefore anxious to submit them to further test, particularly as it is by no means easy to estimate the precise degree of adhesiveness possessed by the red corpuscles within the vessels; and it occurred to me that one means of doing this would be to compare specimens of blood shed from inflamed and healthy parts of the same individual; for if my deductions were sound, the adhesiveness of the red corpuscles ought to be neither more nor less in the one case than in the other.

With this view I made the following experiments. Having carefully examined the blood of a large frog, drawn from a subcutaneous vein of the abdomen, so as to become quite familiar with the appearance of its corpuscles, I applied mustard to the whole surface of one foot till inflammatory congestion had been fully developed in it, and then, amputating both feet at the ankle-joint, squeezed out blood from each upon a glass plate, and carefully examined both specimens, without being able to detect the slightest difference between them. The other experiments with this object were performed on the human subject. In one of these I applied a portion of moistened mustard to the dorsal aspect of the last phalanx of one of my fingers, and retained it there for five hours, with the exception of occasional removal for the purpose of drawing blood for examination. By the conclusion of the time mentioned, the skin on which the mustard had been placed was in a very decided state of inflammation, being red, swollen and painful, and the redness at one spot disappearing imperfectly on pressure, and returning languidly after its removal. A very minute drop of blood drawn with a fine needle from the surface of the most inflamed part was then compared with a drop of similar size from another finger, but no difference could be detected between them, nor had any been observed in previous similar comparisons. On another occasion, a friend of mine suffering from intense inflammation of the back of the hand, in consequence of the irritation of offensive pus, permitted me to take blood with a needle from the most severely affected part, and also from one of the fingers, which was healthy. I compared drops from the two sources several times very carefully with each other by means of the micro-

\* In performing experiments upon a foot in which the circulation has been arrested, it is important to guard against a deception apt to arise from the direct action of an irritant upon the blood in the vessels. Thus, if a drop of chloroform of considerable size be applied to a web under those circumstances, it will soak in and produce its chemical effects upon the blood, the earliest of which is complete abolition of adhesiveness in the corpuscles.

scope, but could discover no difference between them in the adhesiveness of their corpuscles; as indicated by the time of formation of the rouleaux, their mode of grouping, and the tenacity with which the discs composing them adhered when they were stretched. The results of these experiments appear decidedly confirmatory of the conclusion with reference to which they were instituted.

No mention has been hitherto made of the appearance presented by the colourless corpuscles in an irritated part. It is well known that their numbers, in proportion to the red ones, vary very much in different frogs, and it so happened that in the two on which the first mustard experiments were performed they showed themselves but little; nor are they at all conspicuous when the circulation has been arrested by ligature; but in most cases in which irritation is applied to the web while the blood is circulating through it, one of the earliest abnormal appearances is that of white corpuscles adhering in large numbers to the walls of arteries, capillaries and veins, as first described and accurately figured by Dr. WILLIAMS\*. This remarkable phenomenon, though of itself clear proof of an alteration in the properties of the blood in an irritated part, has, strangely enough, attracted little attention from other observers. It is evidently analogous to the change which the red discs experience under similar circumstances. I find that the account commonly given of the white corpuscles in circulation in the vessels of the frog's web, viz. that they may be seen rolling slowly along the walls of the arteries and veins, and sometimes sticking to them, though intended to apply to the state of health†, really describes a condition of a slight amount of irritation, such as is exceedingly apt to be induced by a variety of causes‡. In perfect health the colourless corpuscles are as free from adhesiveness within the vessels as the red discs, but like them assume that property in a degree proportionate to the amount of irritation to which the part has been subjected. When the irritation has been very slight, the white corpuscles, which are susceptible of much greater adhesiveness than the red (as we learn from examining blood outside the body§), acquire some tendency to stick to the vascular parietes, while the red discs still move on in a manner generally regarded as consistent with health, though really lagging slightly behind the liquor sanguinis, and con-

\* Vide *op. cit.*

† Mr. WHARTON JONES, in describing the healthy circulation in the bat's wing, speaks of the colourless corpuscles as "rolling or sliding sluggishly along the walls of the vessels," "both in arteries and veins." He also describes, in the following passage, increased adhesiveness as resulting from irritation. "Towards the end of a protracted sitting, after the web had been much irritated, I have seen, in the venous radicles especially, colourless corpuscles accumulated in great numbers, as we so often see them in the frog." But no stress is laid on this fact as bearing upon the nature of inflammation (see "Observations on the state of the Blood and the Blood-vessels in Inflammation," by T. WHARTON JONES, F.R.S., Medico-Chirurgical Transactions, vol. xxxvi. 1853). Dr. WILLIAMS, supposing that the white corpuscles were always adhesive within the vessels in health, was led to attribute their abnormal accumulation in an irritated part to local fresh formation of those bodies. Vide *op. cit.*

‡ It has been mentioned in the note to p. 660, that this effect is peculiarly liable to be produced in consequence of the vicinity of the warm hand.

§ See page 649.



sequently presenting themselves in somewhat abnormal proportion. I have often observed the complete absence of adhesiveness of the white corpuscles within the vessels in health, and have also watched them gradually assume a tendency to adhere, in consequence of repeated mild applications of chloroform to a web in which they previously exhibited no such disposition whatever. As the irritation increases, the vessels become crusted with them often to a remarkable degree, and occasionally large, colourless, agglomerated masses of them, just such as are seen in blood drawn from the body, may be observed to roll along the large veins among the slowly moving and very numerous red discs. I once watched the formation of one of these masses\* as a delta-like accumulation at the place where a considerable venous branch opened into a main trunk, the calibre of which was nearly entirely occupied by it before it was swept away by the current. As a general rule, the white corpuscles when adhering do not arrest the progress of the red ones, which are often seen to pass through very small intervals among the colourless masses; not unfrequently, however, red corpuscles are stopped in their course and adhere among the white ones, and sometimes, especially in young frogs, capillaries become obstructed throughout their entire length by white corpuscles alone, and when this is the case, they are apt to escape notice from the inconspicuous character of their contents.

The adhesiveness of the white corpuscles, as of the red ones, is limited to the part irritated. A very good example of this presented itself on one occasion when a minute drop of chloroform was applied to a small part of a healthy web so as to induce full dilatation of the arteries and great excess of corpuscles, but without absolute stagnation. It happened that the part affected was supplied with blood by the branches coming from one side of a principal artery; the main trunk being seated just about the limit between the irritated area and the healthy region, the adjacent part of which received supply from the branches of the vessel on the other side. The latter showed no appearance of adhering white corpuscles, nor did the capillaries which were fed by them; but those of the irritated part, though springing from the same trunk, were remarkably encrusted with them from their origin to their minutest ramifications within the area, while the capillaries and veins in the same part were similarly affected. This striking appearance continued for hours after the chloroform had been applied, successive fully formed white corpuscles adhering as they flowed in from the trunk, being evidently affected secondarily to the change induced by the chloroform in the tissues of the web.

Thus the affection of the white corpuscles of the blood in an irritated part is in all respects strictly parallel to that of the red discs, while the greater adhesiveness of which the former are capable, renders the facts regarding them more obvious and unmistakeable.

\* Being desirous to verify the results derived from the frog by observations upon mammalia, in which the aggregation of the red corpuscles assumes a much more striking appearance, I examined the wings of two small bats. In the first specimen, the corpuscles, both red and white, exhibited decided adhesiveness within the vessels, the web being apparently in a state of irritation from injuries which the animal had sustained. In the other there was also some adhesiveness in the part that first met my eye, the red discs tend-

\* This observation was made subsequently to the reading of the paper.

ing to aggregate into rouleaux, and giving a lumpy aspect to the somewhat dark streams in the larger vessels: but turning to another place, I found the blood there of pale tint and perfectly homogeneous aspect; nor could I detect by a careful search any evidence of a tendency on the part of the white corpuscles to stick to the vascular parietes. It happened that there was complete absence of flow in one artery and concomitant vein of considerable size, yet not a rouleau was to be seen either in them or in any of their branches. On the contrary, the red discs lay at about equal distances from each other, uniformly distributed throughout the calibre of the vessels; and this state of things remained unchanged during about a quarter of an hour, in which I continued to observe them in their perfectly quiescent condition. On examination of some blood from the heart of this bat shortly after, the red corpuscles exhibited a very remarkable degree of adhesiveness, such as I had never seen in human blood\*, presenting a glaring contrast with their state within the vessels†.

Thus we may, I think, regard it as fully established, that, in mammalia as well as in amphibia, both the red discs and the colourless globules of the blood are completely free from adhesiveness within the vessels of a perfectly healthy part, but that when the tissues have suffered from irritation, both kinds of corpuscles assume, in proportion to the severity of the affection, a degree of that tendency to stick to one another and to neighbouring objects which they possess when withdrawn from the body, and consequently experience obstruction to their progress through the minute vessels.

And here I cannot avoid remarking, that this principle explains, if it does not altogether reconcile, the discordant opinions of physiologists regarding the causes of the circulation. It shows that while there is, as we have before seen‡, strong ground for agreeing with those who hold that the flow of the blood is due simply to the contractions of the heart, aided, in animals with valved veins, by the actions of the muscles, the respiratory movements, and, in the case of the bat's wing, by rhythmical venous contractions; yet there is also much truth in the view of those who maintain that the tissues of a part, independently of any change of calibre in the vessels, exercise a great influence upon the progress of the blood through the capillaries. For though the tissues do not, as has been hitherto supposed by the latter class of authorities, actively promote the circulation, yet their healthy condition is none the less necessary to it, being essential to the fitness of the blood for transmission by the heart through the minute vessels.

\* The remarkable adhesiveness of the red corpuscles of the blood of this bat, when withdrawn from the body, has been particularly described in Section I., page 649.

† Mr. WHARTON JONES, in the paper before referred to, describes the red discs as aggregating within the vessels of the healthy bat's wing, when their movement is arrested from any cause, in the same manner as in blood removed from the body. *Vide Med.-Chir. Trans. loc. cit.* I suspect that the pressure of the plate of thin glass employed in order to bring the necessarily high powers of the microscope to bear upon the object is apt to irritate the web and give rise to a degree of congestion, characterized by a tendency to aggregation on the part of the red discs and adhesion of the colourless corpuscles to the walls of the vessels. I have observed that results of irritation have shown themselves in the web of the frog when I have used a plate of thin glass in the same manner as with the bat, for the purpose of applying a high power to the pigmentary tissue.

‡ See page 654.



It is an interesting question, whether the freedom of the corpuscles from adhesiveness in health is due to some active operation of the tissues upon the vital fluid, or whether their adhesiveness in an inflamed part or outside the body is the result of a prejudicial influence exerted upon the blood by the irritated tissues, or by the objects of the external world with which it comes in contact when shed. The fact that the non-adhesiveness of the corpuscles within the vessels continues in an amputated limb, shows that it is independent of the central organs of the nervous system, and probably too of any nutritive actions going on in the tissues. Also, if the latter were concerned in its production, we should expect to find the corpuscles adhesive in the large arteries and veins of the webs, since it is doubtless chiefly in the capillaries that the mutual interchanges take place between the blood and the solid elements of the body. It may be difficult to obtain further evidence upon this point, but some light may be thrown upon it by the consideration of the causes of the coagulation of the blood, which seems to be a closely allied subject.

I have shown elsewhere\*, that in mammalia, as well as in amphibia, the blood remains fluid for days in the veins of an amputated healthy limb, though retaining its property of coagulating when shed†. Its fluidity within the vessels is unaffected by free admixture of the atmosphere with it. For example, seven hours after injecting air into the veins of an amputated sheep's foot, I found the frothy mixture contained in the vessels still quite fluid; and the blood which formed the bubbles, coagulated when shed. Again, a human leg having been amputated above the knee, I pressed out the blood from about an inch of the open mouth of the popliteal vein, and covered the raw surface lightly with a damp cloth, so as to guard against drying of the blood, or of the walls of the vessel in contact with it. After the lapse of twenty-four hours, the vessel was still patulous; but the blood, though it had been so long freely exposed to the influence of the air, continued perfectly fluid. Further, if a vein in an amputated sheep's foot is simply wounded, no clot forms except at the seat of wound. If, however, a portion of any ordinary solid matter, such as a fragment of glass, a bit of clean wax, a hair, a needle, or a piece of fine silver wire, be introduced into such a vein, a deposit of fibrine takes place after some minutes upon the foreign body‡, followed by coagulation of the blood in that particular part of the vessel; the coagulum, however, never adhering

\* See a paper by the author "On spontaneous Gangrene from Arteritis, and the Causes of the Coagulation of the Blood in Diseases of the Blood-vessels," *Edinburgh Medical Journal*, March 1858. The observations there recorded, and also the others mentioned in the text with regard to coagulation, have been made since the reading of the original manuscript.

† The blood coagulates more slowly the later it is examined after death or amputation, and finally becomes altogether incapable of the process. The time when this occurs differs in different cases. Thus, in the foot of the sheep I have seen coagulation take place, though slowly, on the sixth day; but in the human subject on one occasion I found the blood remain permanently fluid when shed within forty-eight hours of death, though in another instance at the same period a soft clot formed in about half an hour.

‡ These facts, ascertained in November 1858, have considerably modified the views expressed in the paper above referred to.

to the vein, except at the lips of the wound\*. This shows that an ordinary solid possesses an attraction for the particles of the fibrine, such as is not exercised by the walls of the vessels; or, in other words, that the vascular parietes differ from all ordinary solid substances in being destitute of attraction for that element of the liquor sanguinis.

The blood-vessels are not the only constituents of the animal body which have these remarkable relations to the blood. If the integument of a sheep's foot be partially reflected, and one of the subcutaneous veins immediately wounded, so as to let some blood run into the angle between the skin and the rest of the limb, before any drying of the tissues has occurred, care being taken that no hairs or other solid matters have been introduced, this blood will remain in whole or in part fluid for half an hour or more; whereas, if blood from the same vessel be placed in contact with any ordinary solid, whether on the foot or elsewhere, it will coagulate in perhaps five minutes†. This is sufficient proof that the subcutaneous cellular tissue resembles the lining membrane of the vessels in its conduct towards the blood. The long time during which blood

\* From what has been stated in the text, it is evident that the ammonia theory of Dr. B. W. RICHARDSON does not account for the fluidity or coagulation of the blood within the vessels. But the facts mentioned by that gentleman in the valuable essay which has gained the last ASTLEY COOPER prize, and also my own experience [see the paper before referred to], have convinced me that a certain amount of the volatile alkali does exist in freshly-drawn blood, and that it has the effect of retarding the process of coagulation. This principle must be borne in mind in all experiments upon this subject, in order to understand circumstances which would otherwise be inexplicable. Thus, if the foot of a sheep be obtained with the blood retained in the vessels by a bandage applied before the death of the animal, and, after reflection of the skin, a needle be introduced into a vein by a free opening made by the scissors, a deposit of fibrine will be found upon it in perhaps five minutes; but if the needle be pushed through the coats of such a vein, so as to introduce it without previous wound of the vessel, and allow little opportunity for escape of ammonia, the deposit will not take place for a quarter of an hour or more. Again, the blood obtained by wounding a vein immediately after reflecting the skin, within the first few hours after the death of the animal, takes a much longer time to coagulate the blood shed from the same vessel after the lapse of half an hour or so; doubtless in consequence of escape of ammonia having occurred in the interval. This circumstance seems to prove that the ammonia is free in the blood in its normal condition within the vessels, and not merely liberated during the process of coagulation; for it is to be remembered that the mere wounding of a vein in no way interferes with the fluidity of the blood in it, except at the wound.

† After the blood has lain for some time in the angle between the skin and the limb, it coagulates, if removed from it, much more rapidly than blood freshly shed from a vessel. Thus, in one case, blood let out from a vein was part of it placed at once on a glass plate, and part allowed to run into the angle between the skin and limb. That on the glass plate was not completely coagulated for ten minutes; but that in the other situation, having been left for twenty minutes, and then transferred to the plate, was a consistent clot within six seconds, indeed as soon as I could examine it. This fact seems to me to throw great light upon the subject of coagulation. The sudden transition from perfect fluidity to a coagulum can only be explained, I conceive, on the hypothesis that the ammonia had almost all escaped while the blood lay in the angle; yet this escape had not caused coagulation. Hence it seems to follow, that ammonia is in no way essential to the fluidity of the blood while it is surrounded by healthy tissues. Another point, which the simple experiments upon the sheep's foot show clearly, is that a certain amount of ammonia in the blood will retard without preventing the deposit of fibrine upon a needle or other ordinary solid introduced into the vessels; and it appears very doubtful whether healthy blood ever contains sufficient ammonia to prevent such an occurrence.



has been observed to remain fluid but coagulable in the tunica vaginalis, seems to show that serous membranes are similarly circumstanced; and it appears probable that the same may be the case with other tissues.

But though some of the facts above mentioned furnish clear evidence that ordinary solid matter induces coagulation by an attractive agency, it by no means follows that the tissues are necessarily merely neutral in their conduct towards the blood in this matter. It is quite possible that they may exert an active influence upon it, in consequence of which the particles of fibrine may experience a mutual repulsion, in the same way as would seem to be the case with the pigment-granules of the chromatophorous cells of the frog during the process of diffusion\*. Indeed some such hypothesis seems almost necessary in order to explain the remarkable fact, that the blood coagulates within a few hours of death in the cavities of the heart and great venous trunks, though it retains its fluidity for days in the smaller vessels. Thus in the human subject twenty-four hours after death I have found clots in the heart and larger veins, including the upper parts of the axillary and femoral trunks, but fluid blood in the lower parts of those vessels and all their branches in the limbs. It seemed possible at first that this difference might depend on the position of the great vessels in the thorax and abdomen, where decomposition begins earlier than in the limbs. But this proved not to be the case; for in a horse twelve hours after it had been killed, I found the blood fluid in the intercostal and small cardiac veins, though coagulated in the vena cava and the coronary vein of the heart, which is in that animal of very large size. There being no reason to suppose the walls of the larger vessels differently constituted from those of the smaller ones, or more liable to undergo *post mortem* changes, the natural interpretation of these facts seems to be that the blood has, even within the body, a certain tendency to coagulation, counteracted by an influence exerted upon it by the containing tissues, which, operating to less advantage the larger the mass of the fluid acted on, fail, at least after death, to prevent it from following its natural course in vessels of a certain magnitude. Again, if we suppose that the tissues are merely passive with regard to the blood, it seems difficult to understand the rapid solidification of a large quantity shed into a cup. For we have seen that mere exposure to the atmosphere will not account for the fact; while at the same time the experiments upon the sheep's foot indicate that an ordinary solid has but a very limited range of operation upon the surrounding blood†, and that the clot which it induces does not propagate itself to more distant parts; so that the central portions of such a mass of blood should remain fluid, unless we admit that, when

\* See p. 634 of this volume.

† I find that if a needle is introduced into a vessel and removed after the expiration of about two minutes, before any deposit of fibrine has yet occurred upon it, a certain amount of coagulation nevertheless takes place afterwards in that particular part of the vessel in which the needle had lain. This is a curious circumstance, indicating that an impression leading to coagulation is produced upon the blood by contact with an ordinary solid for a shorter time than causes, during its presence, any visible solidification. The clot, however, is very slow in forming and very incomplete, so that such cases cannot be compared with the perfect and rapid coagulation of a large mass of blood outside the body. Indeed, when blood is drawn into a large cup, a great deal of it never touches the side (the ordinary solid) even for an instant.

shed from the vessels, it is liberated from an influence which previously kept in check a spontaneous proneness to coagulation. Hence it seems likely that a foreign solid introduced into a vein acts not by creating a disposition to aggregate on the part of the fibrine, but by increasing a pre-existing tendency to it (as a thread induces the crystallization of sugar-candy), exalting the mutual attraction of its particles to a degree which overcomes a counteracting agency on the part of the tissues.

Further inquiry will, in all probability, throw clearer light upon this subject, but in the meantime the facts already known furnish to the unaided senses indisputable proof of the fundamental principle to which we were led by microscopical observation, viz. that the tissues through which the blood flows have, when healthy, special relations to the vital fluid, by virtue of which it is maintained in a fit state for transmission through the vessels. Further, the differences of adhesiveness in the corpuscles according as the blood is surrounded by healthy tissues or ordinary matter, can now be no longer matter of surprise, knowing as we do the alterations which take place in the chemical condition of the liquor sanguinis in consequence of such changes of circumstances, and also the great effect produced upon the adhesiveness of the red discs in blood outside the body by slight variations in the quality of the plasma\*.

The freedom from attraction for the fibrine, if not the actual repulsion of it, on the part of the walls of healthy blood-vessels, seems to explain the well-known fact in pathology, that when healthy capillaries are subjected to abnormal pressure in consequence of venous obstruction, the fluid squeezed through their parietes consists almost exclusively of serum; the fibrine being apparently excluded from their pores as liquid mercury is from those of flannel, or any other texture composed of a material destitute of attraction for it.

From the speedy coagulation of lymph effused into the interstices of inflamed organs or upon inflamed serous surfaces, compared with the length of time that blood has been known to remain fluid after being poured out into such situations in a state of health, and also from the deposition of fibrine which occurs at an early period upon the lining membrane of the vessels in arteritis or phlebitis, whether in the limited inflammation which results from the application of a ligature, or in the more extensive affection which is apt to occur spontaneously, it would appear that the liquor sanguinis, like the corpuscles, tends to comport itself near inflamed tissues as if in the vicinity of ordinary solid substances. It is true that coagulation is not observed to occur in the vessels of the frog's web after the application of irritants; but this is accounted for by the length of time required for the occurrence of the process within the vessels, the liquor sanguinis passing on into healthy regions, leaving the adhesive corpuscles behind it. Adhesiveness of corpuscles may, however, come on in circumstances which admit of permanent fluidity of the blood. Thus if a cat be killed without hemorrhage, and one of the jugular veins be exposed and tied in two places, and the animal be then suspended by the head so that the vein may be vertical in position, the upper part of the venous compartment included between the ligatures will within a very few minutes become colourless in consequence of rapid subsidence of the red corpuscles, implying that they are already closely

\* See Section I. p. 650.



aggregated, although, if the skin be carefully replaced so as to prevent drying of the tissues, the blood will remain fluid in that part of the vein for many hours. Whether the adhesiveness of the corpuscles in this case depend on a *post mortem* change in the vessels, or whether it is merely the result of the large size of the vein preventing the tissues from acting effectually on the blood, remains to be determined; but such a fact seems to prove that a higher grade of vital activity, so to speak, is required to prevent adhesiveness of corpuscles than to maintain the fluidity of the blood. Hence it is probable that, even if the blood were at rest in the vessels of a part, a stronger degree of irritation would be required in order to determine coagulation than would suffice to induce adhesiveness of the corpuscles, which seems to be a more sensitive test of a deviation of the tissues from the standard of health. I have however ascertained, by experiments upon the amputated sheep's foot, that if caustic ammonia is applied freely to a part of a vein after pressing the blood out of it, and the blood allowed to return when the ammoniacal odour has passed off, coagulation takes place in the portion of the vessel which has been so treated, although the chemical action of ammonia, if any of it remained in the tissues, would tend to prevent or check coagulation\*. I have also found a similar local clot form, though more slowly, after merely pinching a piece of a vein.

The principal results obtained in this section may be summed up as follows:—

The effects produced upon the circulation by the application of an irritant to a vascular part are twofold, consequent upon two primary changes in the tissues, which, though often concomitant, are entirely independent both in nature and mode of production. One of these is dilatation of the arteries (commonly preceded by a brief period of contraction), giving rise, in proportion to the increase of calibre, to more free flow through the capillaries, the blood remaining unaffected, except in the rate of its progress. This purely functional phenomenon is developed indirectly through the medium of the nervous system, being not limited to the part acted on by the irritant, but implicating a surrounding area of greater or less extent. The other change is the result of the direct operation of the irritating agent upon the tissues, which experience some alteration, in consequence of which the blood in their vicinity becomes impaired, losing the properties which characterise it while within a healthy part, and which render it fit for transmission through the vessels, and assuming those which it exhibits when removed from the body and placed in contact with ordinary solid matter. The first indication of this disorder of the vital fluid is, that its corpuscles, both red and white, acquire some degree of adhesiveness, which makes them prone to stick to one another and to the vascular parietes, and, lagging behind the liquor sanguinis, to accumulate in abnormal numbers in the minute vessels. This adhesiveness may exist, in proportion to the severity of the affection, in any degree, from that which merely gives rise to a very slight preponderance of the corpuscular elements of the blood in the part, up to that which induces complete obstruction of the capillaries; and when the irritation has been very severe, the liquor sanguinis also shows signs of participation in the lesion by a tendency to solidification of the fibrine.

\* See the paper "On Spontaneous Gangrene," &c., before referred to.

## SECTION IV.

*On the Effects of Irritants upon the Tissues.*

The object of the present section is to inquire into the nature of that primary change which we have seen to be produced in the tissues by the direct action of irritants upon them.

The conclusion already arrived at, that blood flowing through an irritated part approaches more and more nearly, in proportion to the intensity of the affection, the condition which it assumes when separated from the living body, naturally leads us to infer that the tissues concerned are in some degree approximated to the state of ordinary matter, or, in other words, have suffered a diminution of power to discharge the offices peculiar to them as components of the healthy animal frame.

This inference is strongly supported by considering what common effect is likely to be produced upon the tissues of the frog's web by all the various agents known to cause inflammatory congestion. To take first the case of mechanical violence. A forcible pinch of the delicate web seems likely, *a priori*, to impair its powers; for if the lesion be sufficiently severe, complete death of the part will result. An elevated temperature proves equally destructive if carried far enough; and its operation to a degree just short of this, while it produces congestion, can hardly fail to cause diminished vigour in the tissues. So also powerful chemical agents, if used cautiously, give rise to inflammation; but if otherwise, kill the part they act on. Even the pungent irritants which do not exert much chemical action, seem to benumb the energies of the spot to which they are applied. Thus a morsel of capsicum placed on the tip of the tongue speedily produces numbness there, and a piece of mustard lying on the finger for an hour or two dulls the sensibility of the skin. Chloroform, too, while it very readily induces stagnation followed by vesication in the frog's web, is an agent which appears likely to benumb the vital energies. If a small frog be put into a bottle of water highly charged with carbonic acid, and removed from it some time after all motion of the limbs has ceased, it will be found that, though the heart is still beating, the blood-vessels of the webs are loaded with stagnant corpuscles. After a while, however, resolution will take place, and some time later the animal will regain its consciousness. Here it appears probable that the carbonic acid, poisoning the web as well as the brain, paralyses for a time the functional activity of both; and that the return of the circulation, like the recovery of the cerebral functions, depends on a restoration of the dormant faculties of the affected tissues.

Perhaps the most instructive case is that of the galvanic shock, which the following circumstances first showed me to be capable of causing inflammatory congestion. Being desirous of ascertaining the effects of galvanism upon the cutaneous pigmentary system, I applied the poles of a battery in rather powerful action to the skin of the head of a frog, when, the shock affecting the brain, the animal was stunned and lay perfectly motionless. This state of things being favourable for pursuing my inquiry by aid of the microscope, I drew down one of the passive limbs, and having placed the foot under



the instrument, arranged the fine platinum wire extremities of the poles at a short distance from one another at opposite sides of one of the webs, so that the current might pass through a part in the field of view, the circulation meanwhile remaining healthy. I now completed the circuit of the battery, when the leg became instantly drawn up by reflex action; yet on re-examination of the web, I found that, momentary as the shock had been, the part through which it had passed had become affected with intense inflammatory congestion, gradually shading off towards the healthy condition, which existed at a little distance. After about a quarter of an hour resolution of the confused mass of stagnant corpuscles occurred, and shortly after this the creature regained the power of voluntary motion. I afterwards repeated the experiment, both upon the same animal and upon another specimen, and always with the same results; and I particularly observed in one case that the white corpuscles were affected with great adhesiveness in the congested region.

With regard to the manner in which the abnormal condition of the blood was brought about in these cases, it has been already mentioned in Section I. that the galvanic current produces no increase of the adhesiveness of the red corpuscles of blood outside the body; but after what has been stated in the last Section, the reader will see no reason to think such an effect likely. It may, however, seem not improbable that the galvanic shock might, by its direct action upon the blood within the vessels, reduce it to the same condition as if removed from the body. But that this was not really the cause of the congestion, was clear from the fact that in the parts less intensely affected, where the corpuscles still moved slowly though possessed of considerable adhesiveness, the same condition continued long after all the blood which was in the vessels when the shock was transmitted had passed away. In this case therefore, as in all the others which we have considered, the blood was affected secondarily to the tissues. This being established, the natural interpretation of these experiments appears to be, that the portion of the web affected was, as it were, stunned by the shock, and its functions suspended like those of the brain; the resolution of the inflammation, like the return of volition, depending on recovery of function on the part of the tissues concerned.

From such considerations as these, it appears that all those agents which produce inflammatory congestion when applied to the web, though differing widely in their nature, agree in having a tendency to inflict lesion upon the tissues and impair their functional activity.

But powerful as are the arguments thus obtained by inference, it is very desirable to confirm them by direct observation, and it fortunately happens that the cutaneous pigmentary system of the frog is a tissue which discharges functions very apparent to the eye, so that it is easy to trace their modifications under the influence of irritation.

In the first experiment with mustard described in the last section (performed September 29th, 1856), the space on which the irritant had acted presented a very striking difference from the rest of the web in the appearance of the pigment, which in healthy parts was in the form of small roundish black dots; while in the mustard area, and accurately corresponding to the extent of stagnation in the capillaries, each spot was extended to a stellate figure.

I thus became for the first time aware that the pigment is capable of variations, and my attention having been directed to the subject, I soon found that similar changes occur spontaneously, and give rise to alterations in the colour of the skin, which is paler in proportion as the colouring matter is more completely collected into round spots. For some weeks I supposed myself to have been the first discoverer of this curious fact, till I was referred by Dr. SHARPEY to the recent labours of the Germans on the subject. They, however, as I afterwards found, had taken an entirely erroneous view of the phenomenon, attributing the round form of the masses of pigment to contraction of the branching offsets of stellate cells; whereas it turned out that the chromatophorous cells do not alter in form, but that the colourless fluid and dark molecules which constitute their contents are capable of remarkable variations in relative distribution, the molecules being sometimes all congregated in the central parts of the cells, the offsets containing merely invisible fluid, while at other times the colouring particles are diffused throughout their complicated and delicate branches; and between these extremes any intermediate condition may be assumed. It further appeared that concentration of pigment takes place in obedience to nervous influence, while diffusion, though also an active vital process, tends to occur when the pigment-cells are liberated from the action of the nerves. But for further particulars on this subject, I beg to refer the reader to the immediately preceding paper in this volume.

The contrast between the pigment in the area on which the mustard had acted and that of surrounding parts in the case last alluded to, at once struck me as probably the result of a direct action exercised upon the tissues by the irritant. It seemed possible, however, that it might be a secondary effect of the state of the blood in the congested vessels; and in order to ascertain which was the truth, I performed, on the 14th of October, the following experiment:—

Having cut out a piece of the web of a healthy frog, I placed a small portion of mustard upon its centre when all the blood had escaped from it. After a while the spots of pigment seen through the thin margin of the mustard, presented a stellate form, while in the rest of the piece they were still of a rounded figure. Hence it was clear that the change in the disposition of the pigment was the result of the direct action of the mustard upon the tissues of the web.

A new field of investigation was thus opened before me, promising to throw great light upon the nature of inflammation.

To explain the effects of irritants upon the pigmentary tissue proved, however, to be a matter of considerable difficulty. Tincture of cantharides and croton oil, which happened to be among the first substances which I employed with reference to this subject, resembled mustard in causing diffusion of the pigment. Taking, in the first instance, the same view of this change as the German authorities, I attributed it to the relaxation of contractile cells, and regarded its occurrence, in consequence of irritation, as an indication of loss of power in the tissues, a view which was in harmony with the nature of the derangement of the blood in a congested part. Croton oil, curiously enough, acted very slowly on the web, not producing any change on either pigment or blood



for an hour or more: also its effects appeared inconsistent with my theory; for while it ultimately gave rise to diffusion of the pigment to even a greater extent than I had seen occur with mustard, yet it induced only comparatively slight appearances of congestion. Chloroform also seemed at first still more anomalous in its operation, though in the opposite way; for though it was pre-eminently potent in inducing congestion, it caused no alteration whatever in the appearance of the pigment, whether mildly or strongly applied.

Afterwards, as the true nature of the pigmentary functions became unveiled, and further facts were developed, these difficulties were completely cleared away. The first step towards their solution was made in an experiment with ammonia. A frog being placed under chloroform, I covered the whole of the foot with sweet oil, except a small area in one of the webs, the pigment being in the stellate condition, *i. e.* about midway between perfect concentration and full diffusion. An assistant then held at a short distance above it a piece of lint soaked in the strongest liquor ammoniæ, so that its pungent alkaline vapour might play upon the exposed area, while the rest of the foot was protected by the oil. This having been continued for a few seconds, accumulation of corpuscles and stagnation occurred in the vessels of the area, without any change in the appearance of the pigment. After a while, however, the creature happened to grow pale, and, in the web generally, the pigment became completely concentrated so as to assume the dotted aspect, but in the part which was the seat of congestion it remained stellate as before. Hence it appeared that though the ammonia did not cause any change in the distribution of the pigment, it had in reality produced a great effect upon the chromatophorous cells, which, in the area exposed to its influence, had been deprived of the power of concentration by the mildest degree of action of the alkali that sufficed to induce stagnation of the blood. On examination of the web about four hours later, resolution of the stagnation was found to have taken place, though there was still some excess of corpuscles, with marked adhesiveness of the colourless ones in the vessels of the ammonia area. The creature was now released for the night. Next morning the integument was in the opposite extreme of colour, being almost black, and the pigment had the reticular appearance, being fully diffused throughout the whole web, except the central part of the ammonia area, where it retained the same stellate condition as the day before. Hence it appeared probable that the diffusive power, as well as the concentrating, had been paralysed by the ammonia, but had been recovered in all the area except the part that was likely to be the last to regain its functions. To ascertain whether the concentrating power had also been regained, I killed the frog and amputated the leg; soon after which the usual *post mortem* concentration took place completely in the web generally, while in the central part of the area the medium state was still retained, and in the rest of its extent concentration considerably beyond the medium state, but short of the full degree, supervened, showing that recovery of function had taken place to a considerable extent, but was not yet quite complete.

I now felt little doubt that chloroform also possessed the power of arresting the pigmentary functions; but in order to prove the fact I killed a dark frog, and placed one

of its legs in that fluid for half a minute, and then wrapped both it and the other leg in damp lint. After some hours the limb which had not been treated with chloroform was quite pale, while the other, having lost the faculty of *post mortem* concentration, remained as dark as before. The appearance presented by the pigment in the two feet is shown in Plate XLVII. figs. 1 and 2.

Mechanical violence proved similar in its effects on the pigment, which, in the area pinched, retained the same appearance as before, except that in parts where the pressure operated most severely the cells seemed sometimes to have suffered rupture. Fig. 2, Plate XLVIII. is a camera lucida sketch of part of a spot which had been compressed by means of padded forceps, with an adjoining uninjured portion of the web. The pigment was fully diffused before the experiment was performed, and remained so afterwards in the area squeezed, while it became concentrated elsewhere, and this was the condition of things when the drawing was made. The concomitant differences in tint between the blood in the affected and the sound parts in consequence of the accumulation of closely packed red discs in the former, are also strikingly shown in the sketch\*.

The galvanic shock, too, produced no effect apparent to the eye upon the pigment of the parts in which it caused stagnation of the blood, but experiments afterwards made showed me that, like ammonia, it exerted a paralysing agency both upon the concentrating and the diffusive powers; and the same results ensued on the application of dry heat in the cases mentioned in the last section.

From these and other similar facts it appeared that mustard, croton oil, and cantharides are exceptional as regards the diffusion to which they give rise, the usual course being that irritants, when applied so as to produce stagnation of the blood, suspend at the same time both the functions of the pigment-cells.

It afterwards turned out that mustard was, in reality, no exception to this general rule. Subsequent experiments showed that diffusion takes place to very different degrees in different instances under the action of this substance, but that in all cases, after reaching a certain point, it becomes incapable of advancing further in the irritated part, however much it may increase in the body generally, in case of the animal changing to a darker colour. These differences depend partly upon the strength of the mustard, the diffusion being least when the irritant is most potent. Thus, on one occasion, when a solution of the volatile oil in spirit of wine was applied to a web in which the pigment was fully concentrated, congestion was very rapidly developed, without any alteration in the appearance of the chromatophorous cells. That the diffusion is

\* Much more gentle pressure, if long continued, may give rise to similar results, as I happened to notice in the following manner. Being desirous of watching the process of *post mortem* concentration of the pigment, I amputated a leg of a dark frog, and, having stretched out the foot over a glass plate, put a small piece of thin glass upon part of one of the webs, and applied a high power of the microscope to it. I was disappointed to find, however, that the change I wished to observe did not take place; but on looking at other parts of the web, found that immediately beyond the edge of the slip of thin glass, the pigment was on all sides considerably concentrated, although remaining fully diffused where the glass covered it; an effect which I could attribute only to the gentle squeezing to which the two plates subjected the part of the web that lay between them.



in inverse proportion to the energy with which the mustard acts, was well illustrated by the experiment which furnished the drawing given in Plate XLVIII. fig. 1\*. In that case, a frog having been prepared in the manner mentioned in the note to page 611, a portion of very strong mustard was placed upon the middle of one of the webs, the pigment being in the stellate condition, such as is seen on the left-hand side of the sketch, which represents a part of the edge of the spot to which the irritant was applied, together with an adjoining portion of the web. Shortly after this had been done, I noticed that the pigment was in a state of full diffusion in a ring round about the opaque mass, producing the reticular appearance shown in the stripe down the middle of the sketch. I had in a previous case seen a similar ring become affected with congestion, when a portion of mustard had been applied for a long time, in consequence of the pungent vapour of the volatile oil playing upon the neighbouring parts of the web, and there could be no doubt that the effect on the pigment in the present instance was due to the same cause; but in the latter no material change was as yet visible in the blood except close to the edge of the mustard, where the corpuscles were seen to be abnormally adhesive. After the lapse of about an hour, the area on which the irritant had lain being examined, was found to be the seat of the most intense inflammatory congestion, indicated in the drawing by the crimson colour of the vessels, but the pigment there had experienced only an exceedingly slight degree of diffusion, being, in fact, almost exactly in the same state as at the commencement of the experiment. Thus the vapour of the volatile oil, though operating too mildly to cause inflammatory congestion, nevertheless induced the highest possible degree of pigmentary diffusion; but the mustard, where it lay actually in contact with the web, and acted energetically upon it, arrested that very process of diffusion to which its gentler operation gives rise.

In the progress of the case it happened that the animal changed from the medium tint which it had at first to a very pale colour, the pigment, in the web generally, assuming the dotted condition depicted on the right-hand side of the drawing. Yet many hours after the mustard had been removed, the pigment on which it had acted retained its stellate disposition, and the reticular appearance in the surrounding ring also remained unchanged, showing that the power of concentration had been permanently lost in those parts, and affording a favourable opportunity for obtaining by means of the camera lucida a delineation of the medium, and both extreme conditions of the pigment in the same web. Next day the experiment was rendered still more instructive by the skin becoming excessively dark, the pigment undergoing full diffusion in the healthy parts of the web, so that the contrast between the ring about the congested area and the surrounding regions no longer existed: yet the stellate condition was still maintained where the mustard had lain, showing that it had suspended the faculty of diffusion no less than that of concentration.

Croton oil now no longer seemed anomalous in its operation. Its curiously slow action upon the frog is comparable to the mild influence of the vapour of mustard, and the slight amount of inflammatory appearance which I had sometimes observed in a

\* This experiment was performed subsequently to the reading of the paper

part where it had caused a great degree of pigmentary diffusion, is strictly analogous to the healthy state of the circulation in the reticular ring round the congested area in the last experiment.

Cantharides also presents a parallel case. Its action is even more slow than that of croton oil; and on referring to notes taken at an early period in this investigation, I find that in one instance, when two hours and a half had elapsed after the application of a small drop of the tincture to the web, though diffusion of the pigment had become apparent in the area on which it had acted, no change of the blood had yet been observed; and an hour and a half later, the red corpuscles, though abnormally adhesive as compared with those in surrounding parts of the web, were still moving slowly through the vessels.

Hence it appears that diffusion of the pigment may be produced by either of these three substances without the blood undergoing any material derangement, and therefore that its occurrence under their influence is to a great extent, if not entirely, independent of the inflammatory process. On the other hand, it has been demonstrated, as regards mustard, that when stagnation of the blood has been developed through its action, the state of the pigment-cells is the same as is induced by irritants generally, viz. a complete suspension of functional activity; and, from analogy, we may be pretty sure that this is also true of croton oil and cantharides, although their slow operation renders it difficult to obtain absolute proof upon the point.

In a physiological point of view, it is an interesting question, what is the cause of the diffusion of the pigment induced by these three irritants. I have shown elsewhere\* that concentration is the invariable result of the action of the nerves upon the chromatophorous cells, and that diffusion takes place whenever they are liberated from nervous influence. Also in the tree-frog of the Continent, which is much more liable to changes in the colour of the integument, in consequence of direct irritation, than our own species, the invariable experience of the German observers was, that concentration followed the application of a local stimulus, while secondary diffusion sometimes occurred in the irritated spot, depending apparently upon exhaustion†. From these facts, diffusion ensuing on irritation cannot well be regarded as an increased action excited by the stimulus, but rather as an evidence of diminished vigour. With croton oil and cantharides, which have not an irritating vapour, the diffusion is exactly limited to the extent of the irritant, showing that it is due to a direct action on the tissues; and the most probable explanation of its occurrence appears to be that mustard, croton oil, and cantharides have the peculiarity among irritants of affecting the nerves of the pigment-cells in the part they act on, somewhat more rapidly than the cells themselves, and, paralysing the former while the latter still retain their powers more or less intact, permit diffusion to go on unrestrained by nervous influence, till the further operation of the irritant completely suspends the pigmentary functions. It may be objected to this view, that diffusion occurs on the application of these substances to an amputated limb, but, from evidence given elsewhere‡, it is probable that the pigment-

\* See the paper "On the Pigmentary System," page 641.

† See page 627.

‡ See page 640.



cells possess a local nervous apparatus, on which the occurrence and maintenance of *post mortem* concentration depend, and the paralysis of which, while the pigment-cells retain their powers, would give rise to diffusion in an amputated limb. Be this as it may, the fact that the state of full diffusion continued in the ring around the congested area in the last mustard experiment for hours after the irritant had been removed, although, during that time, complete concentration occurred in the web generally, is pretty clear evidence that the pigment-cells in that part had not merely been stimulated to increased action (for in that case they would have returned to their former condition soon after the stimulus had ceased to operate), but had suffered a loss of the faculty of concentration. Whether the loss of power resided in the nerves of the pigment-cells, or in those cells themselves, is a matter of indifference as regards the objects of the present inquiry; the important fact being that an action of the mustard so mild as to give rise to little or no derangement of the blood, nevertheless produced a certain degree of loss of power in the part on which it operated. There can be no doubt that the same principles apply to the cases of croton oil and cantharides; and thus the diffusion caused by these three irritants assumes a high interest, as visible evidence of diminished functional activity accompanying, if not preceding, the earliest approaches to inflammatory congestion in parts which have been subjected to their influence.

With the view of ascertaining the nature of the effect produced on the pigment-cells by the mildest action of chloroform which is capable of causing inflammatory disorder, I ascertained, by repeated experiments, the shortest time in which the vapour of that liquid gave rise to unequivocal signs of a congestive tendency in the web of the living frog; and having found this to be about half a minute, suspended one of the legs of a recently killed dark frog in a vessel, the bottom of which was covered with chloroform, having previously examined the webs microscopically, and found that full diffusion of pigment existed throughout them. The result was that the limb exposed to the chloroform vapour remained dark, while the other became gradually pale. On re-examination of the former after some hours, each web presented stripes of full diffusion of pigment alternating with others in a medium condition; their direction being at right angles to the margin of the web. The longitudinal folds in which the webs had happened to be, had prevented the chloroform vapour from gaining equally free access to all parts; yet the chromatophorous cells in the stripes that had been thus partially protected from its influence had been incapable of complete concentration, showing that even the exceedingly slight degree of action which the chloroform could have exerted upon these places sufficed to diminish, though not to destroy, the functional activity of the pigmentary tissue.

In one of the experiments performed in order to determine the effect of mechanical violence, as before alluded to, the pigment remained unchanged for days in the area which had been pinched, while varying in other parts of the web; yet, though great excess of red corpuscles existed in the vessels of the affected spot, they never ceased to move; showing that the functions of the pigment-cells might be completely suspended by a degree of irritation short of that which occasions actual stagnation of the blood.

The same thing was afterwards\* seen in a case in which a small drop of wood-vinegar was placed upon one of the webs of a frog which had been deprived of the power of voluntarily moving the limbs by passing a knife between the occiput and the atlas, so as to sever the brain from the cord. The fluid being thus allowed to lie quite undisturbed, did not spread at all upon the web, which was dry before it was applied. It produced its effects very slowly, so that, after the lapse of three and a half hours, the blood in the area covered by it, while everywhere presenting inflammatory appearances, was still only partially stagnant. Yet throughout this space the pigment retained exactly the same moderate degree of diffusion as it had at the beginning of the experiment, although in the interval complete concentration had taken place elsewhere; and a very striking contrast was presented between the stellate pigment with the adhesive though still moving blood-corpuscles where the web was wet with the vinegar, and the dotted pigment and perfectly healthy circulation in the dry parts immediately adjacent.

Seeing, then, that complete suspension of the pigmentary functions may be caused by an amount of irritation which induces only a minor degree of congestion, and further, that (as we learn from the experiment with chloroform vapour) a still milder operation of an irritant renders these functions sluggish though not completely arresting them, we seem to have sufficient evidence that impairment of the functional activity of the chromatophorous cells occurs in the very earliest stages of that primary change in the tissues which leads to inflammatory derangement of the blood.

It was seen in the ammonia experiment related above, that resolution having taken place in the congested area, the pigment-cells of the part recovered the faculty both of diffusion and concentration. This might have been pretty confidently predicted; for as congestion is a necessary consequence of the disorder produced in the tissues by irritants, we might have been almost sure that the return of the vital fluid to that healthy condition in which it is fit for free transmission through the vessels, must be preceded by a restoration of the living solids to their normal state. In the case alluded to, however, no sign of recovery of the pigment-cells appeared till after the circulation had become re-established; and even when several hours had elapsed, they still remained paralysed in the central part of the area on which the ammonia had acted. This is in harmony with the fact lately pointed out, that complete suspension of the pigmentary functions may accompany a state of the blood short of actual stagnation; and both appear to depend upon the circumstance that the chromatophorous cells are an extremely delicate form of tissue.

The rate of recovery of the pigment-cells varies greatly, however, in different cases, and in this respect much depends upon the nature of the irritant. An example of an agent of this class producing only very transient effects on the pigmentary functions is presented by carbonic acid. It has been before mentioned that the immersion of a living frog for about a quarter of an hour in water highly charged with that gas, gives rise to complete stagnation of the blood in the webs, although the heart still continues beating, but that resolution occurs after the animal has been exposed for awhile to the

\* This experiment was performed subsequently to the reading of the paper.



atmosphere. With a view to ascertaining whether the congestion was due to the direct action of the acid upon the tissues, I made the following experiment. Having killed a dark frog and amputated both legs, and ascertained by microscopic examination that the pigment was fully diffused in the webs, I put one limb into a bottle of "aërated water" and the other into ordinary water: the latter soon became pale through *post mortem* concentration, but the former remained as dark as ever during the two hours for which it was retained in the solution of carbonic acid, the direct action of which upon the bloodless tissues was thus demonstrated. An hour after the limb had been taken out, however, it was evidently recovering, being distinctly lighter in colour than it had been, and two hours later it was quite pale, and the pigment in the webs was found to be in almost the extreme degree of concentration. In subsequent similar experiments I left the leg in the aërated water for a longer time, during which it always retained precisely the same tint that it had when first introduced; and, if left for many hours, showed signs of loss of vitality, by the early supervention of cadaveric rigidity and exfoliation of the epidermis; but if it was taken out within about four hours, the pigment-cells recovered completely; and in one case a leg not removed for nine hours regained, nevertheless, to a considerable extent, the faculty of concentration\*. Thus it appears that carbonic acid, though exercising a powerful sedative influence upon the tissues, and paralysing for the time their vital energies, so as to give rise to intense inflammatory congestion, yet, even after a very protracted action, leaves them in a state susceptible of speedy recovery.

Here we see for the first time a satisfactory solution of the much-debated problem of the cause of congestion of the lungs in Asphyxia; for there can, I conceive, be no doubt that the pulmonary tissues, exposed under ordinary circumstances to the influence of a free supply of oxygen, suffer, like those of the frog's web, from the vicinity of an abnormal proportion of carbonic acid, and inflammatory congestion is the necessary consequence. At the same time, the rapid recovery of the lungs from asphyxial congestion of considerable duration, when the normal atmosphere is readmitted, finds an equally close parallel in the speedy return both of the pigment-cells and the blood to the healthy condition when the foot of the frog is removed from the aërated water.

But the most important lesson to be learnt from these simple experiments with carbonic acid upon amputated limbs, is that the tissues possess, independently of the central organs of the nervous system, or of the circulation, or even of the presence of blood within the vessels, an intrinsic power of recovery from irritation, when it has not been carried beyond a certain point; a principle of fundamental importance, which has never before, so far as I am aware, been established or conjectured. It applies equally in the case of other irritants. Thus having transmitted for about a quarter of a minute, through one of the webs of a dark amputated limb, powerful galvanic currents, such as I had before ascertained to cause stagnation of the blood when operating for an instant upon the living animal, I found, after the lapse of an hour and a quarter, that the pro-

\* This observation was made subsequently to the reading of the paper.

cess of concentration had advanced considerably in the next web, but in that on which the galvanism had acted had only just commenced, even in the parts most remote from the point to which the poles of the battery were applied; while in the vicinity of that spot the state of full diffusion still continued. After the lapse of three more hours, however, the pigment was almost fully concentrated in the part of the web where it was before only slightly so; and even where it had been most directly subjected to the galvanic influence, it had undergone a certain, though very slight degree of the same change, the chromatophorous cells having even there partially recovered their functions.

This inherent power in the tissues of recovering from the effects of irritation, explains the occurrence of resolution in an amputated limb, such as I once observed in a case where a moderate amount of congestion had been induced under the action of oil of turpentine before the animal was killed, and the blood resumed to a great extent its normal characters in the vessels several hours after the limb had been severed from the body.

The return of the blood along with the tissues to the state of health is a very interesting circumstance. Whether it depends upon an intrinsic power of recovery on the part of the vital fluid, or on the living solids resuming an active operation upon it, is at present uncertain; but in the mean time, the phenomena of resolution already assume a far more intelligible aspect than heretofore, on the hypothesis that the tissues generally are endowed with the same faculty of self-restoration as the pigment-cells.

It may be well to give here a list of all the agents whose effects upon the pigmentary functions I have investigated. They are as follow:—Mechanical violence, the galvanic shock, desiccation of the tissues\*, dry heat, warm water at 100° FAHR., intense cold, caustic ammonia, a strong solution of common salt, carbonic acid, acetic acid, tincture of iodine, chloroform, oil of turpentine, mustard, tincture of cantharides, and croton oil.

These are all of them irritants, *i. e.* give rise to inflammatory congestion through their direct action upon a vascular part, as I have witnessed in the frog's web in every case except that of cold, the influence of which in causing intense inflammation in the human subject is, however, familiar to all†. All of them also afforded, in their effects upon the pigment-cells, ocular evidence of impairment of the functional activity of the tissues on which they act; and considering the number included in the list, and their great variety in essential nature, we need not hesitate to admit that similar effects are produced by the entire class of irritants.

There is another tissue in the frog's web which discharges functions apparent to the eye, viz. the arterial muscular fibre-cells, the contractions of which are readily recog-

\* The effects of deficiency of moisture in the web were observed in amputated limbs, in which I have seen both suspension of pigmentary functions from this cause and recovery from that state after the application of water. While the circulation is going on in the living animal I have not found desiccation of the web to occur, unless the tissues had been weakened more or less by irritation.

† The only experiment which I made with cold was performed by introducing a test-tube, containing a dark amputated limb, into a freezing mixture of ice and salt at about 20° FAHR. for ten minutes. When the frozen limb had thawed, I ascertained, on microscopic examination, that the pigment had undergone a slight degree of *post mortem* concentration, but five hours later it was still in much the same condition.



nized in consequence of the changes of calibre which they produce in the vessels; and the manner in which the arteries are affected in a congested part of the web indicates that the muscular, like the pigmentary tissue, has its functional activity impaired by a certain amount of irritation. Thus I have repeatedly been struck with the fact, and noted it before I knew its significance, that an artery running through a limited area on which an irritant has acted, remains dilated in the spot, although it may vary in other parts of its course. This I have observed in one experiment with mustard, in one with acetic acid, in two with ammonia, and in one with heat. In the last-mentioned case the appearance was particularly striking, from the circumstance that two arteries happened to pass through the burnt part, and were constricted to absolute closure in the rest of their course, contrasting strongly with their fully dilated state within the area.

In the ammonia experiments also the artery concerned was, in the progress of each case, seen to be completely constricted beyond the congested area, though still dilated within it. The limitation of this effect on the arteries, to the extent of the part acted on by the irritant, proves that it is the result of its direct action on the tissues; differing remarkably in this respect from the dilatation of the vessels, which is produced indirectly through the medium of the nervous system, and affects a wide space round about the spot irritated.

But with regard to both the muscular fibre-cells of the arteries and the pigment-cells, it may fairly be questioned whether the diminution of power to act resides in them or in those portions of their nerves which are situated in the irritated region. The view that the nerves are paralysed by irritants is consistent with the benumbing influence well known to be exerted upon the human skin or mucous membranes by some of those agents, *e.g.* mechanical violence, the galvanic shock, cold, and chloroform. I have also observed, as before alluded to\*, that mustard produces a similar result on the cutaneous sensory nerves, and hence it seems probable that the same is true of the whole class of irritants. Again, the diffusion induced by mustard, croton oil, and cantharides indicates, according to what we have seen to be its most probable explanation, that the nerves of the pigment-cells suffer impairment of functional activity under the action of these three substances. On the other hand, the fact that diffusion is arrested equally with concentration by most irritants, appears to prove that the chromatophorous cells are themselves also affected with loss of power; for, as has been before alluded to, the withdrawal of nervous influence from them in a healthy state of the tissues invariably gives rise to diffusion, and the same result would necessarily follow the action of an irritant which merely paralysed the nerves. I have also observed, on two occasions, after the energetic operation of an irritant upon a part of a web containing a large artery†, that drawing

\* See page 677.

† The main arteries lying between the layers of skin of which the web consists, are not so speedily acted upon by irritants as the capillaries of the dermis. This is most marked in large frogs with thick webs. In one such specimen, a drop of chloroform caused first stagnation and then discoloration from chemical action on the blood in the capillaries of the dorsal layer of the web to which it was applied, while a main artery

the point of a needle firmly across the vessel failed to induce the slightest contraction in it, even at the very point crossed by the needle; proving that the muscular fibre-cells had lost their irritability. At the same time it is by no means improbable that the nerves of the arteries may suffer before their muscular constituents, just as in the intestines, after death, the functions of the intrinsic nervous apparatus are lost some time before muscular contractility ceases\*.

The question whether the suspension of function induced by irritants is confined to the nerves or affects the tissues generally, being one of great interest, I was anxious to obtain clear evidence regarding it; and it occurred to me that valuable information would probably be derived from observing the effects of such agents upon the action of the cilia, which, though not present in the web of the frog, exist in abundance upon the mucous surfaces of the mouth and œsophagus of that animal. Dr. SHARPEY, in his celebrated article "Cilia" in the 'Cyclopædia of Anatomy and Physiology,' mentions experiments made by PURKINJE and VALENTIN, and also by himself, with a great variety of substances, including among the rest some irritants, which, when applied with sufficient energy, arrested completely, by their chemical action as it was supposed, the movements of the lashing filaments. It is evident, however, that in order to produce effects at all comparable to the state of the tissues of the frog's web in congestion, it would be necessary to adopt some more delicate method of experimenting, and the most eligible means for this purpose seemed to be to allow an irritating vapour to play upon a ciliated surface. Accordingly, on the 30th of November, 1857†, having cut off a small piece of the tongue of a frog killed about an hour before, and placed it upon a slip of glass under the microscope, with just enough water to permit the free play of the cilia, I held near to it a piece of lint soaked in chloroform, keeping my eye over the microscope. The effect was instantaneous cessation of the previously rapid action of the cilia, which now stood out straight and motionless, like the hairs of a brush. I now immediately withdrew the lint, after which the same state of complete inaction continued for about half a minute, when languid movements began to show themselves, and after the lapse of five minutes more the ciliary action was going on pretty briskly in some parts, and ten minutes later seemed to have almost completely recovered.

Thus chloroform vapour produced in the ciliated epithelium-cells a condition precisely similar to that brought about in the pigment-cells by irritants applied so as to cause inflammatory congestion of the web, viz. a state of suspension or temporary deprivation of functional activity. And as the removal of the epithelium-cells from the surface on which they grow does not arrest the movements of their cilia, no mere paralysis of nerves

lying beneath still contained blood of natural appearance, and showed evidence of languid contractility, while in the capillaries of the plantar layer of the web, the circulation was still going on in a pretty healthy state. This frog, however, seemed endowed with unusual powers of vitality in the tissues. This observation, as well as that in the text to which this note refers, was made subsequently to the reading of the paper.

\* See the paper 'On the Functions of the Visceral Nerves,' before referred to.

† This date indicates that the experiments on the cilia have been performed since the paper was read.



could account for this result, which necessarily implied that the epithelial tissue itself was affected with loss of power to discharge its accustomed functions. In repetitions of this procedure upon the same and other portions of the tongue, I did not generally get complete cessation of movement of all the cilia, but usually some retained a languid action, which improved after the chloroform had been removed. In one instance, however, the same perfect stoppage took place as in the first case, and the recovery was also very general, though the returning action was languid. Under these circumstances, a piece of lint dipped in strongest liquor ammoniæ was brought within about  $1\frac{1}{2}$  inch of the object, and retained there for about fifty seconds, during which time the ciliary motion became progressively and greatly diminished, and within twenty-five seconds of the removal of the lint, had ceased altogether. Some water was then added, so as to get rid of the absorbed alkali, when the cilia soon began to move again, and within about three minutes their play was more vigorous and general than before the ammonia was used, and three minutes later it was universal, as it was prior to the application of the chloroform. On another occasion, in a different animal, the cilia having been ascertained to be in rapid motion on a fresh piece of tongue, lint containing liquor ammoniæ was held at a short distance from it for thirty-three seconds. The cilia very soon grew languid, and by the end of the time mentioned had quite ceased to act. The lint was at once withdrawn, but no recovery occurred; the operation of the irritant had been rather too energetic, and the vitality of the tissue had been destroyed. A languid state of the cilia was also produced by placing freshly prepared mustard near them, and improvement took place when it had been removed; but the essential oil itself, applied on lint like the chloroform and ammonia, though not acting so rapidly as might have been expected, permanently arrested the vibratile filaments. The vapour of strong acetic acid, if acting for four seconds, caused great diminution of the motion, and in another instance arrested it completely in five seconds. I did not, however, see any recovery from the effects of this agent, which produced obvious organic injury in the cells. The introduction of a portion of the mucous membrane of the mouth into a bottle of aërated water for about twenty minutes gave rise to permanent stoppage of the cilia, and similar treatment for three or four hours caused disorganization of the epithelium, whereas the same period of immersion in ordinary water did not arrest the cilia. Powerful interrupted galvanic currents, transmitted for a few seconds through a particular spot in a piece of tongue on which the cilia were in free movement, abraded a portion of the epithelium there, and arrested completely the cilia of adjacent cells still *in situ*, and rendered those of other parts of the specimen extremely languid in their action. But the most satisfactory results were obtained from experiments with heat, which has the great advantage over chemical irritants, that it leaves no material behind it to act upon the delicate tissue. On the 14th of December, 1857, having ascertained that steeping a piece of the tongue of a frog for five minutes in water of  $110^{\circ}$  FAHR. caused total and permanent cessation of ciliary action and desquamation of the epithelium, at 9<sup>h</sup> 9<sup>m</sup> P.M. I placed a portion of that organ, in which the vibratile movements were equable though rather languid, in water at  $100^{\circ}$  FAHR., and retained it there for a minute and a quarter, when it was trans-

ferred to cold water. On examining it after the lapse of nearly two minutes, I found the cilia acting decidedly more briskly than at first, but in the course of the next quarter of an hour they flagged very much, and in many parts ceased to move altogether. By this time I had fixed the specimen securely at the bottom of a glass trough, which I now suddenly filled up with water at  $102^{\circ}$  FAHR., and on first catching sight of the object, within a quarter of a minute of this procedure, found all the cilia absolutely motionless. I then at once drew off the warm water with a siphon previously arranged; and no sooner had this been done, than movements already began to show themselves in the cilia, and their action increased rapidly on my filling up the trough with cold water, and in a short time was all but universal and brisk, far superior to what it was before the hot water was put in. After a few minutes more, however, it was again very languid, and ceased entirely in many parts. I now, at  $9^{\text{h}} 38^{\text{m}}$ , filled up the trough with water at  $104^{\circ}$  FAHR.: at  $9^{\text{h}} 38^{\text{m}} 17^{\text{s}}$  the cilia were almost all motionless; by  $9^{\text{h}} 38^{\text{m}} 55^{\text{s}}$  the trough had been again emptied, but at  $9^{\text{h}} 39^{\text{m}} 5^{\text{s}}$  there was even less movement seen. Cold water was again poured in at  $9^{\text{h}} 39^{\text{m}} 35^{\text{s}}$ , and after eighteen seconds, action was reappearing in the cilia, and it continued to increase during the next seven minutes, at the end of which time it was again almost universal. At  $9^{\text{h}} 52^{\text{m}}$  the cold water was drawn off, and the same condition of the cilia having been ascertained to exist, the trough was, at  $9^{\text{h}} 52^{\text{m}} 27^{\text{s}}$ , filled up again with water at  $104^{\circ}$  FAHR.; eighteen seconds after this had been done, the ciliary action was found much diminished, but had not fully ceased; and after nine seconds more, during which the warm water was drawn off, the cilia were still acting very slightly. Within twenty-three seconds of this time the trough was again filled with cold water: now, however, the epithelium was in many parts beginning to exfoliate, swelling up by endosmose in obedience to the ordinary laws of chemical affinity, and so indicating that it was losing its vitality. I also lost sight of the precise spot which I had been observing, but noticed that ciliary action was again going on pretty quickly in some places. There can be no doubt, although there was no opportunity for observing the fact, that the first immersion in hot water caused cessation of the ciliary action; and that being admitted, we have in this case suspension of function and recovery four times repeated in the same fragment of tissue in consequence of as many applications and withdrawals of the irritant. It is a curious circumstance that each recovery, except the final one, brought up the action of the cilia for a time to a better state than they had just before the last introduction of warm water. But the discussion of this and other circumstances in this case will be best reserved till after the mention of another set of experiments.

In order to eliminate the nerves completely from among the causes both of the suspension of function produced by irritants and the recovery from that state, it seemed desirable, if possible, to observe those occurrences in detached epithelium-cells, and on the 22nd of January 1859 I made the attempt to do so. At first, however, it proved more difficult than I had anticipated. It was of course easy to obtain the material to operate on, by gently scraping the surface of the palate of a recently killed frog with a knife, and placing the mucus-like product on a plate of glass with a drop of water. But the



tissue thus separated from its connexions was in an exceedingly delicate condition, and any agent used for arresting the action of the cilia was very apt to destroy at the same time the vitality of the cells. Thus when the object was warmed by placing the glass plate on a piece of iron at about 100° FAHR. for half a minute, the vibratory movements were arrested, but never recovered, and in a short time the cells swelled up by endosmose. It appeared probable that the tissue had suffered during the time required for the cooling of the glass; and in order to avoid this, and also prevent the object-glass becoming obscured by vapour from the warm water condensing upon it, the epithelium was placed between two slips of thin covering glass, kept from too close approximation by fragments of the same material interposed, the whole forming a layer so thin that it would be rapidly heated if any hot body were placed in its vicinity, and cool as quickly on its removal. A small cautery iron, with a bulbous extremity about as big as a hazelnut, just too hot to bear in contact with the finger, was now put behind the stage of the microscope, within about three-quarters of an inch of the object, the diaphragm plate having been removed to afford room for this being done without interfering with the light sent up by the reflector. The result, which I watched from the first, was the same that I had once before observed from the very gentle application of heat to a portion of a frog's tongue, viz. primary increase in the action of the cilia which had previously been languid\*, but which, within ten seconds of the approximation of the cautery, were moving with great rapidity, and continued to do so for about twenty-five seconds, at the expiration of which their motion was seen to be diminishing, and after another minute and a half it was considerably more languid than at the beginning of the experiment. The cautery being now removed was found to be much cooled though still warm, and its withdrawal did not affect the cilia, which still remained much in the same state after the lapse of eight minutes. I now repeated the experiment upon a fresh portion of epithelium, but this time used the cautery red-hot, placing it about 2 inches behind the object: no sooner had this been done than the action of the cilia became excessively increased, but this did not continue for more than five seconds, when they became perfectly motionless. The hot iron was now at once withdrawn, but the cilia under special observation did not recover. In other situations in the same specimen, however, movements were observed in the course of the following minute, and it was still continuing seven minutes later, when a part having been brought into the field where there were two considerable groups of cells in moderate activity, the cautery was again applied at a distance of about 2½ inches. The motions of the cilia immediately became distinctly increased, but, as in the former case, this condition gave place in five seconds to universal quiescence. The iron was then removed, and on re-examination after three minutes, the cilia were again moving, though in a somewhat languid manner in both

\* Professor WEBER of Leipsig observed several years ago that the action of cilia upon epithelium cells removed from the human nostril was increased by gentle warmth, but retarded by cold. In that case the elevated temperature was natural to the tissue, and might be supposed to operate by restoring it to its normal conditions. In the cold-blooded reptile, however, the accelerated movement under the influence of heat has, of course, a very different significance.

parts of the field. For the sake of confirmation I again operated in a similar manner upon another specimen, on which I performed no less than five successive experiments with similar results in all. In the first three of these trials I had the very same cilia under observation, and saw them time after time become first increased in action and then arrested under the influence of the cautery, and gradually recover after its removal. In some instances the times of cessation and of recovery were noted as follows:—In the first the cilia were arrested in two seconds after the application of the hot iron, but the exact time of recovery was not observed; in the second, cessation of movement was produced in two seconds, and return began in fifteen seconds; in the third, cessation was in fifteen seconds, and recovery also in fifteen seconds; in the fourth, the times were not noted; in the fifth, movement ceased in about two seconds and returned in twenty. The experiments were performed within about five minutes of each other, or sometimes less. It is also to be remarked, that there were some slight differences in the degree of heat of the cautery and its vicinity to the object.

These experiments are as instructive as they are simple and easy of performance. They show conclusively that a component tissue of the animal frame may, independently of the nervous system, have its actions either excited or paralysed by the direct operation of an irritant upon it, and that it may possess an equally independent power of recovery. Also in the accelerated movements of the cilia elicited by very gentle heat, as compared with the cessation of their vibrations under a higher temperature, we have a striking confirmation of the view which I had taken of the relaxation of the arteries and hollow viscera in consequence of nervous irritation\*. For the law which we thus see regulating the effects of heat upon the epithelium-cells is precisely that which I had inferred must govern the action of afferent nerves upon nerve-cells; this law being, that an agency which, when operating mildly, stimulates a tissue to increased activity, may, when more energetic, temporarily arrest its functions. Whether or not the converse always holds, viz. that any agent which is capable of suspending the functional activity of a tissue may also excite it if applied with sufficient gentleness, or, in other words, whether irritants are in all cases also stimulants, seems very doubtful. As regards the nerves, such does appear to be the case; for while many, and probably all influences which induce inflammatory congestion cause temporary paralysis of sensation in parts on which they act severely enough, they all stimulate the afferent nerves in the first instance, as is shown by the reflex changes in the calibre of the arteries which occur round about any irritated spot. The nervous centres, too, present an illustration of the same principle, not only in the effects produced upon them by the nerves, as lately alluded to, but also in the excitement well known to be occasioned by small doses of many sedative narcotics, such as alcohol, opium, and chloroform, which may be regarded as special irritants of the nervous centres. In the case of the cilia, I have not observed primary increase of movement to be induced by any agent besides heat; but I am not prepared to say that it might not by careful management be made to occur with some other irritants.

\* Vide *antea*, p. 666.



The pigment-cells in the common frog give very little indication of the stimulating properties of irritants, as is evident from several of the experiments which have been recorded in this section. In the tree frog, however, as we are informed by the German authorities, a part of the integument subjected to such influences rapidly assumes a pale tint, and that even in a portion of skin removed from the body. I have also several times noticed, after pinching the web of a common frog, that, although in the spot actually squeezed, the pigment-cells were deprived of their power of changing, a pale ring about one-sixteenth of an inch in breadth has gradually formed in its immediate vicinity in the course of the next hour; whence it seems probable that direct irritation tends to excite concentration in the English species as well as in the continental, but that in the former the effect is developed much more slowly, so that it is apt to pass unnoticed. I further, on one occasion, saw *post mortem* concentration greatly accelerated by heat\*. It is doubtful, however, whether these results are due to direct action upon the pigment-cells; for in the tree frog, as well as in the English kind, the pale tint was not confined to the precise spot operated on, but affected a limited area of surrounding tissue; whence it seems likely that it is developed through the medium of a local nervous apparatus contained in the skin†. If this be true, we have no proof that the pigment-cells are capable of being stimulated except by nervous influence, although they are, as we have seen, peculiarly susceptible of suspension of function through the direct operation of irritants upon them.

With regard to the nature of the change experienced by the tissues when temporarily deprived of power by irritants, the primary increase of motion of the cilia, lapsing into quiescence, under the operation of heat, may suggest the idea of exertion followed by exhaustion. But that the state of incapacity is not dependent on previous action, seems clear from the fact that in the pigment-cells it is maintained and aggravated by an irritant continuing in operation after complete suspension of function has been induced, the same kind of effect being still produced upon the tissues which are unable to act as upon healthy parts. As an illustration of this, I may revert to the results of immersion of an amputated limb in aerated water. The carbonic acid, as we have seen, entirely pre-

\* This observation was made as follows:—On the 2nd of December, 1857, having amputated the legs of a dark frog, I put them both into water of 100° FAHR., but removed the left limb within six minutes of its immersion and placed it in cold water, leaving the right for a quarter of an hour longer, at the end of which time it was considerably paler than the left, and the microscope showed that its pigment was more concentrated. But while the warm water had accelerated the process of concentration up to a certain point, it had ultimately paralysed the pigment-cells and rendered them incapable of further change; so that the right limb remained permanently of the same colour as when removed from it, whereas in the left, which had been subjected for a much shorter time to the noxious agency, concentration continued to advance, so that in twenty-five minutes that leg was as pale as the other, and after an hour more it was a good deal the lighter of the two. I may further mention that rigor mortis was already carried to the extreme degree in the muscles of the right limb when taken out of the water, but in the left this change did not commence till about twelve hours later. At this period the pigment in the left limb still showed signs of retaining its functions, while that in the right had a dirty, indistinct appearance, indicating that it had lost its vitality.

† See the paper 'On the Cutaneous Pigmentary System,' before referred to, p. 640.

vents the occurrence of *post mortem* concentration, implying that the powers of the chromatophorous cells are completely suspended by it within a few minutes at most of its first acting on the part; yet, however long the tissues thus paralysed are kept subjected to its influence, they remain without any sign of action. They will, however, recover speedily and completely if soon taken out and exposed to the air, so that the irritating gas may be dissipated; whereas if retained for several hours in the aërated water, they may, indeed, have their powers restored to a certain extent on removal from it, but exhibit only very feeble action. Such facts as these prove conclusively that the tissues may have their functional activity impaired without loss of vitality by the direct action of irritants, independently of any stimulating effects which may be at first produced by them; and also that the influence thus exerted is of an injurious tendency.

The imperceptible transition from suspension of function to loss of vitality displayed by the long-continued operation of carbonic acid upon the pigment-cells is also well illustrated by some of the experiments upon the cilia, especially those with heat and ammonia, which, unless employed with extreme caution, not only permanently arrested the vibratile filaments, but reduced the epithelium-cells to a condition in which they were amenable to the ordinary laws of chemical affinity. All irritants appear to be agents which, if operating with sufficient energy, completely destroy vitality, probably by inducing, through chemical or physical action, an irreparable derangement of the molecular constitution of the tissues. Their essential property, however, is that of causing, when applied somewhat more mildly, a minor degree of disturbance or disorder in the component textures of the body, which are rendered for the time being unfit for discharging their wonted functions\*, though afterwards, by virtue of their innate powers, capable of spontaneous recovery, the rapidity and completeness of which bears an inverse ratio to the intensity and duration of the previous irritation. Lastly, these same noxious agents, if in a still more gentle form, operate, upon some of the tissues at least, as stimulants, rousing them to increased exertion of their vital functions. How this effect is brought about must, I believe, be only matter of uncertain speculation, so long as the real nature of life in the animal frame remains, as it probably ever will remain to our finite capacities, an impenetrable mystery.

It is an interesting circumstance that, in the experiments with warm water, the cilia, after recovering from the state of quiescence, moved for a while more briskly than they did immediately before the application was made. This increased action cannot be attributed, like the primary acceleration resulting from very gentle warmth, to a mild operation of the irritant; for the epithelium-cells must have been completely cooled down before it commenced. It must therefore be regarded as a true reaction on the part of the tissue, whether dependent on accumulation of vital energy during the period of suspended function, or excited, as by an irritant, by the state of disorder which the warm water had induced, seems uncertain.

\* The word "irritant" is etymologically ill adapted to express the possession of this property; but as it is universally employed in professional nomenclature, it is perhaps best to continue to use it.



Considering the number and variety of the functions which direct observation has shown to be suspended by irritants, viz. pigmentary concentration and diffusion, ciliary motion and nervous action, it appears probable that all the vital processes are liable to similar temporary arrest.

Different tissues, however, seem to differ in the facility with which they are affected by irritants. The pigment-cells are very susceptible to their influence, as is indicated by the complete paralysis which we have seen to be produced in them by agencies that give rise to only a minor degree of inflammatory congestion; and also by the circumstance which I have often observed in the web of the frog, that, as in the choroid coat of the human eye, they become absorbed in parts which have been injured, having been deprived of vitality by causes which inflicted on other textures only a recoverable lesion. The epithelium-cells, too, are very sensitive to irritation, exhibiting its results more rapidly than can be accounted for merely by their exposed situation. In those which invest the mucous membrane of the mouth, the cilia with which they are provided furnish the opportunity of which we have availed ourselves, of observing the stage of suspension of function in consequence of very gentle treatment; and though the epidermis does not admit of this, it shows the further stage of loss of vitality by exfoliating after an amount of injury from which the immediately subjacent tissues readily recover. JOHN HUNTER was unquestionably correct in the opinion that the elevation of the cuticle in vesication depends not only on the effusion of serum beneath it, but on a primary separation arising "from a degree of weakness approaching to a kind of death in the connexion between the cuticle and cutis\*." For I find that in an amputated limb free from blood, although no effusion of serum can occur, the epidermis becomes speedily loosened in a part to which an irritant is applied, as for example, in a web treated with oil of turpentine, whereas it remains elsewhere firmly attached for days if the weather be cool.

The temporary abolition of the normal relations between the blood and the tissues in inflammatory congestion†, must be added to the list of instances of suspension of vital properties by irritation. The tissues the healthy state of which seems most likely to be essential to that of the vital fluid, are those contiguous to it, viz. the walls of the blood-vessels; and that these are really deprived of their vital endowments during inflammation, seems implied by the character of the material which is transmitted through them in that condition. For we have seen that the vascular parietes differ, in the state of health, from all ordinary solids in being destitute of any attraction for the fibrine, if not positively repelling it‡, and that this is probably the cause of the merely serous character of the effusion which takes place in mechanical dropsy depending upon abnormal pressure of the blood within healthy vessels. On the other hand, the exudation of the liquor sanguinis in its integrity, such as occurs in severe inflammation, cannot, I think, be satisfactorily explained by the mere abnormal pressure of the blood pro-

\* Works of JOHN HUNTER, PALMER's edition, vol. iii. p. 349.

† See close of last section.

‡ Vide *antea*, p. 674.

duced by dilatation of the arteries and concomitant obstruction in the capillaries; but seems naturally accounted for on the hypothesis that the walls of the vessels, like other tissues, lose, for the time, in inflammation, their vital properties, and, acquiring an attraction for the fibrine like that exercised by ordinary solids, permit it to pass without opposition through their porous parietes.

It may be well to present a brief summary of the principal results arrived at in the present section.

It appears that the various physical and chemical agents which, when operating powerfully, extinguish the life of the constituents of the animal body, produce by a somewhat gentler action a condition bordering upon loss of vitality, but quite distinct from it, in which the tissues are, for the time being, incapacitated for discharging their wonted offices, though retaining the faculty of returning afterwards, by virtue of their own inherent powers, to their former state of activity, provided the irritation have not been too severe or protracted. This suspension of function or temporary abolition of vital energy is the primary lesion in inflammatory congestion; the blood in the vicinity of the disabled tissues assuming the same characters as when in contact with ordinary solid matter, and thus becoming unfit for transmission through the vessels; while the return of the living solids to their usual active state is accompanied by a restoration of the vital fluid to the healthy characters which adapt it for circulation.

#### CONCLUSION.

It remains to glance at the application of the principles established in the preceding pages to human pathology.

The *post mortem* appearance which is universally admitted to indicate that the early stages of inflammation have occurred during life, is intense redness, depending essentially not upon peculiar distension of the vessels with blood, but upon abnormal accumulation of the red corpuscles in their minutest ramifications. A beautiful example of this condition, developed idiopathically, was presented by the case of incipient meningitis mentioned in the Introduction, in which the vessels of an affected spot of pia mater were filled with a crimson mass of confusedly compacted corpuscles, exactly as in an area of the frog's web to which mustard has been applied. The derangement of the vital fluid in the human subject being thus closely parallel to that which we have studied in the batrachian reptile, we can hardly doubt that in the former, as in the latter, the living solids are in a state of more or less complete suspension of functional activity during inflammatory congestion. This view is supported by the effusion of liquor sanguinis in its integrity in the more advanced stages of the disease in man, and by the speedy coagulation of fibrine upon inflamed serous surfaces, or in the interior of vessels affected with arteritis or phlebitis. For these circumstances, as has been before remarked, appear to indicate that the tissues are for the time being reduced still more towards the condition of ordinary solid matter. These arguments, derived from the appearances of the blood,



are further corroborated by the immediate transition which is apt to occur from intense human inflammation to gangrene\*.

But a comprehensive and complete account of the inflammatory process must embrace not merely the state to which the tissues are brought when the disease is fairly established, but also the causes which lead to it.

Inflammation is sometimes brought about in man in a way strictly analogous to that in which we induce it in the web of the frog's foot, viz. by the immediate operation of some noxious agent from without, as when boiling water is poured upon the skin. One peculiarity connected with such cases, as compared with those which are of idiopathic origin, is the great rapidity with which the various stages of the disorder are often developed. This, however, is the natural consequence of the direct manner in which the prejudicial influence is exerted upon the tissues; the inflammatory phenomena supervening more speedily in proportion to the energy of the irritant. This principle is well illustrated by the effects of mechanical violence upon the human integument. A moderate degree of pressure applied continuously gives rise, during the first few hours, to nothing more than inflammatory congestion, which disappears soon after the pressure has been removed, as seen in the red mark produced upon the forehead by a tightly-fitting hat. But if such treatment be continued for a considerably longer period, vesication will result, as when apparatus employed for the treatment of fractures is applied too firmly for many hours together over a bony prominence. The same effect which is thus slowly developed under a moderate degree of mechanical irritation, may, however, be induced very rapidly through the same agency in a more intense form, as is shown by the bullæ which are often observed in surgical practice very soon after the infliction of a severe contusion. Here the source of irritation being no longer in operation, there is no blush of redness in the vicinity dependent upon arterial dilatation, and hence such cases are often supposed to have nothing in common with inflammation; and I have known these vesicles mistaken for evidence of gangrene, so as to lead to unnecessary amputation. The suddenness with which inflammatory œdema arises in consequence of the bites or stings of venomous reptiles is explicable on the same principle. The poison appears to diffuse itself among the tissues so as to operate directly upon them, and when extremely virulent, kills them outright; but when less potent, produces merely a temporary though rapid prostration of their vital energies with consequent inflammatory effusion. Again, the congestion of the lungs, which comes on so quickly in asphyxia, has been before alluded to†, as probably the result of the sedative influence which, from experiments upon the frog, we are led to believe must be produced upon the pulmonary tissue by the abnormal amount of carbonic acid in the air-cells.

In the class of cases hitherto considered, the derangement of the part, and the causes which lead to it, being both, to a considerable extent, understood, the disease may, I think, be regarded as in so far satisfactorily explained. But one important lesson taught

\* The degenerations of tissue which result from inflammation, ably delineated by Mr. PAGET in his 'Lectures on Surgical Pathology,' are additional evidence in the same direction.

† See page 687.

by the results of this investigation is, that it is necessary to draw a broad line of demarcation between inflammation produced by direct irritation, and that which is developed indirectly through the medium of the nervous system, whether in the immediate vicinity of a source of irritation, as around a tight stitch in the skin, or a thorn in the finger, or at a distance from the disturbing cause, as when the kidneys are affected in consequence of the passing of a bougie, or the lungs through exposure of the feet to cold. Nothing can better illustrate the importance of this distinction, than what takes place in a recent wound. In consequence of the injury inflicted by the knife, together with the subsequent manipulation and exposure, the tissues, in a thin layer at the cut surface, are thrown into that condition which leads to effusion of liquor sanguinis, the fibrine of which, speedily coagulating, remains to constitute the bond of primary union, while the serum trickling away between the lips of the wound produces the discharge which soaks the dressing during the first twenty-four hours. But neither during the exudation of the lymph in such a case, nor during its subsequent organization, is there necessarily any inflammation induced in the lips of the wound through the nervous system; and if this complication does occur, it interferes with the healing process in a degree proportioned to its intensity. In other words, while a certain amount of inflammation as caused by direct irritation is essential to primary union, any degree of it as induced indirectly is both unnecessary and injurious.

The question how inflammation is developed through the medium of the nervous system, possesses a high degree of interest, in consequence of its bearing upon the manner in which counter-irritation operates therapeutically. In the integument, where we have the opportunity of seeing the affected part, the first indication of the supervention of inflammatory disorder around a centre of irritation is a blush of redness, which, as before shown\*, consists, in the first instance, of mere dilatation of the arteries with rapid flow of blood through the capillaries. It is quite conceivable that arterial dilatation, carried to an extreme degree along with powerful action of the heart†, may so increase the tension upon the tissues as to impair their powers gradually by mechanical irritation, just as the frontal integument is affected by long-continued gentle pressure from without, as above alluded to; for we know that when inflammation does exist, mere increase of tension upon the blood in the vessels will greatly aggravate the disorder, as when an inflamed foot is kept in a dependent posture. Supposing this to be the whole mechanism of the disease, its origin would be sufficiently intelligible; for we have seen that vascular dilatation caused by irritation operating through the medium of the nervous system appears to depend on a depressing influence produced by excessive action of the afferent nerves upon the ganglia which preside over the arterial contractions. There are, however, some circumstances, such as the dryness of the nostril which may exist in the early stages of coryza, and sudden suppression of urine in consequence of

\* See page 665.

† It is to be observed, that in the frog, when full dilatation of the arteries lasts for days together without the production of inflammatory congestion, the state of the vessels has been brought about by a very serious operation which greatly weakens the action of the heart.



urethral irritation in cases where renal congestion becomes ultimately established, which seem to indicate that other functions as well as arterial contraction may be primarily arrested by nervous agency in the early stages of inflammation. The study of the pigmentary system of the frog has afforded proof that other tissues besides muscular fibre are under the control of the nerves, and it seems not unlikely that gland-cells or other forms of tissue may, like nerve-cells, be reduced to a state of inactivity by excessive nervous action; and thus we seem to have a clue to comprehending what at first appears anomalous, that prostration of the vital energies of the part actually inflamed may be brought about by unusually great activity in the parts of the nervous system specially concerned with it. This, however, is a wide subject, which requires further investigation. But in the mean time we may, I think, consider as satisfactorily established the fundamental principle, that whenever inflammatory congestion, or, in other words, that disturbance of the circulation which is truly characteristic of inflammation, exists in any degree, the tissues of the affected part have experienced to a proportionate extent a temporary impairment of functional activity or vital energy.

#### EXPLANATION OF THE PLATES.

##### PLATE XLVII.

illustrates the anatomy and physiology of the cutaneous pigmentary system of the frog.

Figs. 1 and 2 are sketched from webs of different feet of the same animal. The creature was dark when it was killed, but one of the legs afterwards underwent the usual *post mortem* change to a pale colour, and such was its state when fig. 2 was drawn. The other limb was deprived of the power of thus altering by immersion for half a minute in chloroform; and fig. 1 shows the appearance of the colouring matter in the permanently dark condition of the integument.

Fig. 3 represents two chromatophorous cells with the pigment-granules fully diffused, the animal having been at the time coal-black. The bodies of the cells are seen to be pale, containing chiefly colourless fluid, while some of the finest branches of the offsets are quite black, in consequence of the dark molecules being closely packed together in them. In the same figure a capillary fully distended with blood-corpuscles is also given.

Fig. 4 represents the colouring matter in the same two cells during the progress of the process of concentration. The dark molecules are already for the most part collected about the middle of the body of each cell; but in the very centre of each cell is a pale point, where the granules seem not yet to have insinuated themselves between the cell-wall and the nucleus. The same capillary is here seen much reduced in calibre.

Fig. 5 shows the pigment in the lower of the two cells, concentration being still further advanced.

In fig. 6 the process is seen to be almost absolutely completed, the molecules being almost all of them aggregated into a black circular mass, occupying the middle

of the body of the cell, the more circumferential parts of which contain only colourless fluid, and are therefore invisible.

Fig. 7 is an outline of the wall of a large blood-vessel, with chromatophorous cells in its external coat. The pigment is almost completely concentrated, but the form of the section of the black masses, where they are seen edgewise, shows that they are not spherical, but disc-shaped.

Figs. 8, 9, and 10 are drawn, with a much higher power, from young frogs, with small pigment-cells: they exhibit especially the form and relations of the nucleus.

In fig. 10 the pigment is shown in an unhealthy state, the molecules being irregularly aggregated.

### PLATE XLVIII.

represents the effects produced by irritants upon the pigmentary tissue and the blood-vessels of the frog's foot.

Fig. 1 shows the results of the application of mustard to the web. The pigment was at first in the stellate condition as on the left-hand side of the sketch, and it remained permanently in that state in the part on which the mustard lay, while at the same time intense inflammatory congestion was produced there, indicated by the deep red colour of the vessels. Just beyond the edge of the mustard the irritating vapour of the volatile oil gave rise to full diffusion of the pigment (an effect peculiar to mustard and a few other irritants when acting mildly), but without material inflammatory disorder of the blood; as seen in the stripe down the middle of the drawing. During the progress of the case the animal changed to a pale colour in the body generally, assuming the dotted aspect depicted on the right-hand side of the sketch in all parts which had not been acted on by the mustard, and thus deprived for the time being of the power of concentration. It will be observed that the blood-vessels of the healthy part are not materially smaller than those of the congested region; the deep colour of the latter being due to their containing closely-packed red corpuscles, while the former are pale in consequence of the blood within them having the normal proportion of colourless liquor sanguinis.

Fig. 2 illustrates the effects of mechanical violence. The lower half of the sketch represents part of an area in one of the webs of a dark frog, which was pinched with a pair of padded forceps so as to give rise to inflammatory congestion. The animal afterwards grew much paler, so that in healthy parts the pigment assumed the angular or slightly stellate appearance shown in the upper part of the drawing. But on the particular spot on which the mechanical violence had operated, the chromatophorous cells being incapable of discharging their usual functions, the pigment remained in the fully-diffused state in which it was at the commencement of the experiment.